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ANNOUNCEMENT

Beginning with the January, 1953, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, the editorial management will be conducted by Dr. Howard C. Taylor, Jr., and Dr. William J. Dieckmann as co-editors. After a period of service of thirty-three years as Editor-in-Chief, Dr. George W. Kosmak will retire from this post but continue to serve in an advisory capacity.

An Advisory Committee on Policy has been formed, the members of which have been selected from societies for which the JOURNAL serves as the official organ of publication. A general advisory group will continue to act as consultants in the acceptance of contributions.

Attention is called to necessary changes for the submission of manuscripts to be noted in the January issue.

It is believed that the generous support accorded to the JOURNAL by the profession in its formative and subsequent years will be continued. The profession is assured that its interests will be dominant in the conduct of this now well-established Journal by both the editors and the publishers.

American Gynecological Society

Transactions of the Seventy-Fifth Annual Meeting

Hot Springs, Virginia, May 12 to 14, 1952

(Continued)

THE EFFECT OF PREOPERATIVE RADIATION OF ADENOCARCINOMA OF THE ENDOMETRIUM*

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PREOPERATIVE irradiation of endometrial carcinoma has been widely adopted as a valuable therapeutic means of improving the end results of treatment of this disease. The plan of irradiation, total tumor dose, and sequence of the therapy differ considerably in various clinics. The recovery rate also varies according to the thoroughness of the plan of treatment and the meticulous precision with which the plan is executed. According to Stowe,[15] microscopic study of uteri removed following such irradiation reveals persistence of apparently viable tumor in from 12.5 to 89 per cent of cases. It is assumed, therefore, that the dose of irradiation delivered to the tumor in comparable clinical groups and pathological grades is the important factor. Improvement of radiation technique at the Radiumhemmet in Stockholm was credited by Heyman[4] as increasing the cure rate of endometrial carcinoma from 44.6 per cent to 61.9 per cent.

Studies aimed at evaluating a form of therapy must define the irradiation dose delivered to the tumor, the microscopic grade of the tumor under consideration, and the clinical extent of the disease at the time therapy was begun. In this way we can evaluate the efficacy of such a plan of treatment by comparing the end results thus obtained with end results obtained in treating tumors similar in extent and cell type by other methods. If inadequate irradiation dosage is delivered to the tumor-bearing area, then very little benefit is to be expected from the preoperative therapy, and such findings should not be used to support the contention that such treatment does not add to the surgical removal of the organs.

The present study was undertaken to evaluate a specific technique, previously described,[10] of irradiating the uterus, parametria, and pelvic lymphatic areas, and to report the effect on the tumor and determine in particular the cure rate in those patients in whom active tumor could no longer be demonstrated on serial section of the removed organ and its appendages.

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

Material

There has been no selection of patients in this study as it comprises all cases admitted to the gynecologic service of the Mercy Hospital Institute of Radiation Therapy. Patients applying for admission are accepted irrespective

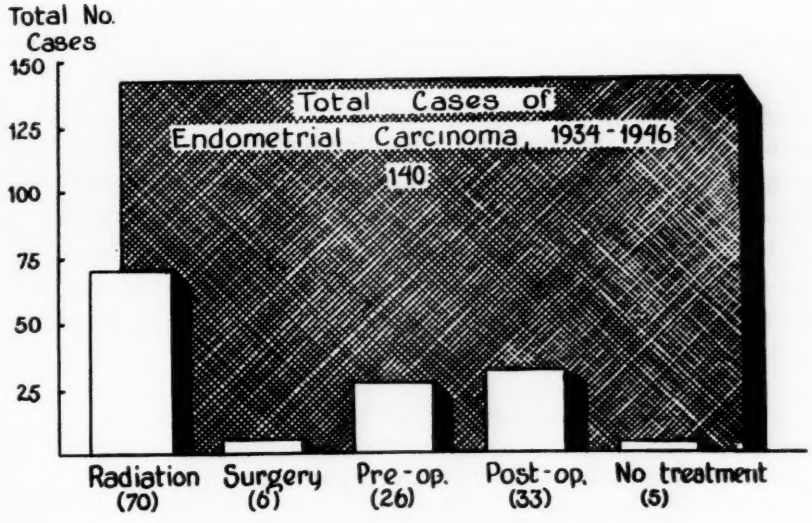

Fig. 1.

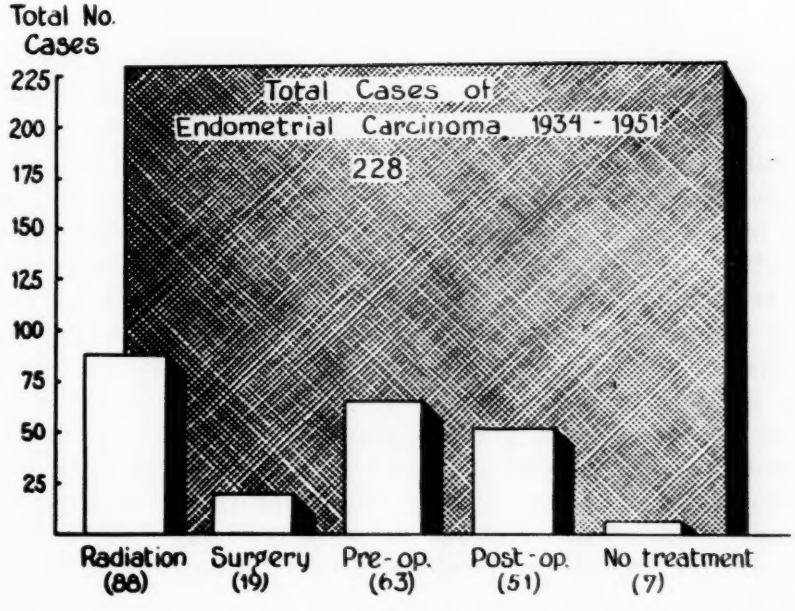

Fig. 2.

of the extent of the disease or previous therapy. The material was limited to that of the tumor service and not the general hospital so that the therapy in the primary cases could be carried on by the same individuals using the same technique. Table I and Fig. 1 show the cases admitted since the radium applicator now in use was first employed and x-ray therapy in the range of 800 to 1,000 kv. was available and prior to 1946.

TABLE I. CASES OF ENDOMETRIAL CARCINOMA, 1934-1946

RADIATION	SURGERY	COMBINED		NOT TREATED	TOTAL
		PREOP.	POSTOP.		
70	6	26	33	5	140

As is to be expected in any unselected series, many previously treated and far-advanced cases are included. This limits the number of cases suitable for a planned therapy. Those patients receiving irradiation only either refused postirradiation surgical treatment or complicating disease made it unwise to attempt surgery. Those patients receiving postoperative irradiation were subjected to the operative procedure by colleagues who then referred the patient for immediate adjunct therapy. In order to obtain more uteri for study as to the effect of irradiation on the carcinoma, cases admitted during the years 1947 to 1951 are included in Table II and Fig. 2. These cases, of course, are not included in the survival studies.

TABLE II. ALL CASES OF ENDOMETRIAL CARCINOMA, 1934-1951

RADIATION	SURGERY	COMBINED		NOT TREATED	TOTAL
		PREOP.	POSTOP.		
88	19	63	51	7	228

Plan of Treatment

At the time of the diagnostic curettage, the Y radium applicator is placed in the uterine cavity; the width of the uterine cavity and amount of radium to be used have been determined as previously described.[10] We agree with Arneson[1] that external irradiation offers an advantage, if given first, but when the tumor has been disturbed by the obtaining of a biopsy, the immediate application of the radium has a more rapid effect on the tumor cells. The radium is removed when 2,000 mg. hr. have been delivered and is reinserted twice more at eight-day intervals. On the days the radium is not in the uterine cavity, x-ray therapy through multiple ports is given, as described in our report of the irradiation technique.[12] Reinvading the uterine cavity has not proved undesirable but advantageous. Antibiotics are employed to prevent sepsis. Dilatation of the cervical canal prevents pyometra or hematometra and careful biopsy furnishes us with samples of tumor tissue which enable us to determine the irradiation effect on the tumor cells. If, for previously determined, valid reasons, surgical removal of the uterus and its appendages is not to be undertaken, then further periodic curettage is done to determine tumor activity. Negative curettage, however, is not accepted as evidence that the tumor has been destroyed in every instance.[5]

It is never our plan to employ surgical treatment alone; in the 19 cases so listed postoperative irradiation was refused. As stated, the patients receiving postoperative x-ray therapy had been subjected by our colleagues to immediate hysterectomy at the time the diagnosis was made. As the material is available for study and the irradiation and follow-up are supervised by the authors, the procedure can be accurately evaluated.

It is our plan to offer every patient the advantages of palliative x-ray therapy, irrespective of the extent of the disease. In 7 cases this was refused by the patient.

Dosage

Fig. 3 portrays the radium applicator in place.

In Fig. 4 the equal intensity curves as published by Schmitz[11] have been drawn in and they show that the intensity attained at the periphery of the uterus is 4 S.E.D. if 50 mg. of radium elements are inserted in each arm and the stem and applied for 14 hours at eight-day intervals for a total dose of 6,300 mg. element hours. Hence, the distribution of the radium intensities with the Y applicator seems to be very homogeneous and will attack the entire carcinoma if limited within the boundaries of the uterus.

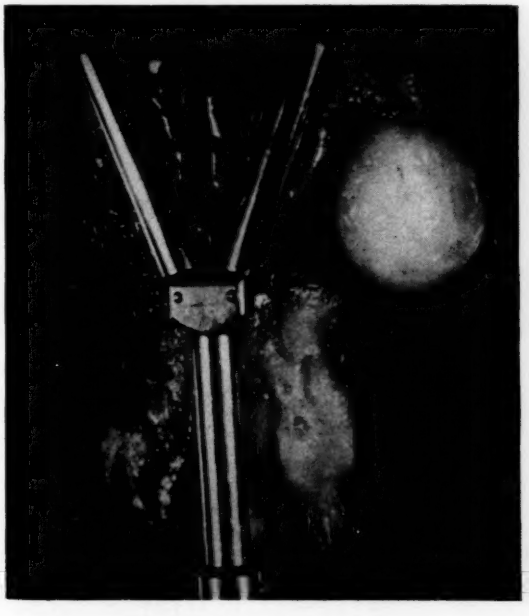

Fig. 3.

X-ray therapy is applied through multiple ports so arranged as to shield the bladder and rectum from overdosage. It is our aim, however, to irradiate the parametrial tissues and pelvic lymph nodes.

It is never positively known after a physical examination whether a carcinoma of the cervix or uterus has extended by metastasis to the lymph vessels and the regional lymph nodes. The surgeon always performs the radical panhysterectomy and lymph node dissection regardless of the size of the primary growth. The radiologist should plan to execute a "radical extended" radiation technique which should include the parametria and the regional lymph nodes. Therefore, the combined technique with roentgen and radium rays is indicated in all clinical groups.

Radiation Changes

After removal of the uterus and its appendages, routine sections were made and the absence of carcinoma established according to the technique

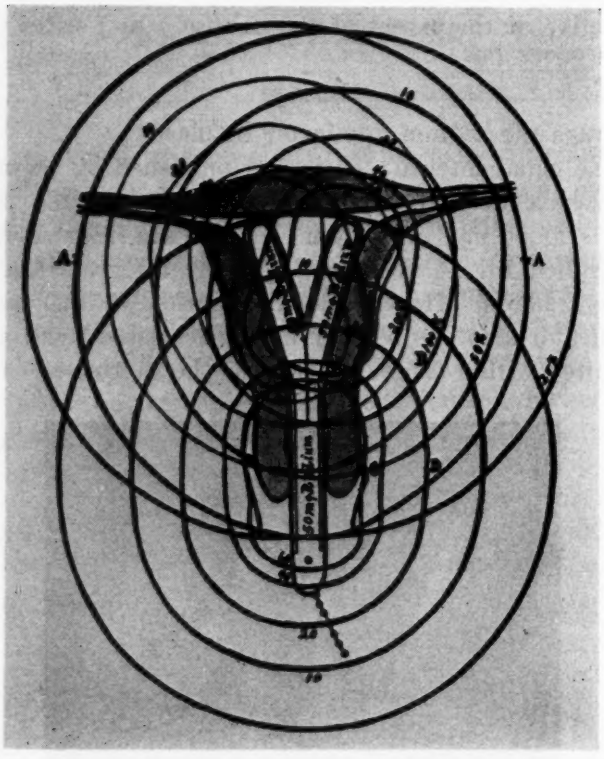

Fig. 4.

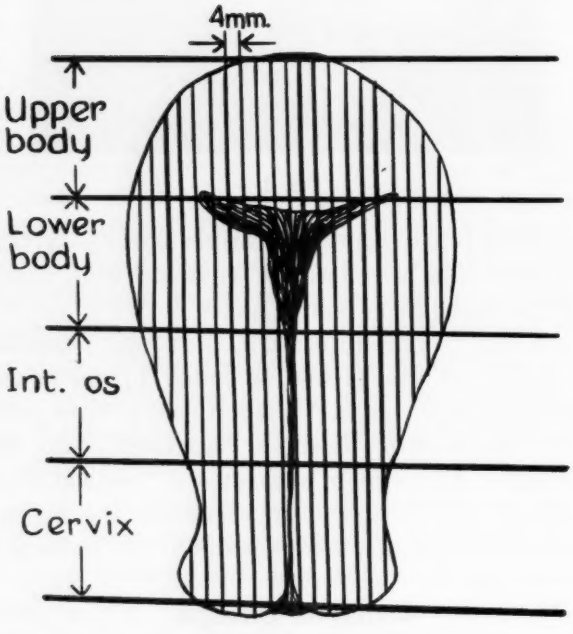

Fig. 5.

developed in preparation of our previous report.[14] The following details are an abridgment of the more extensive description referred to. Later three parallel transverse incisions passing completely through the uterus were made.

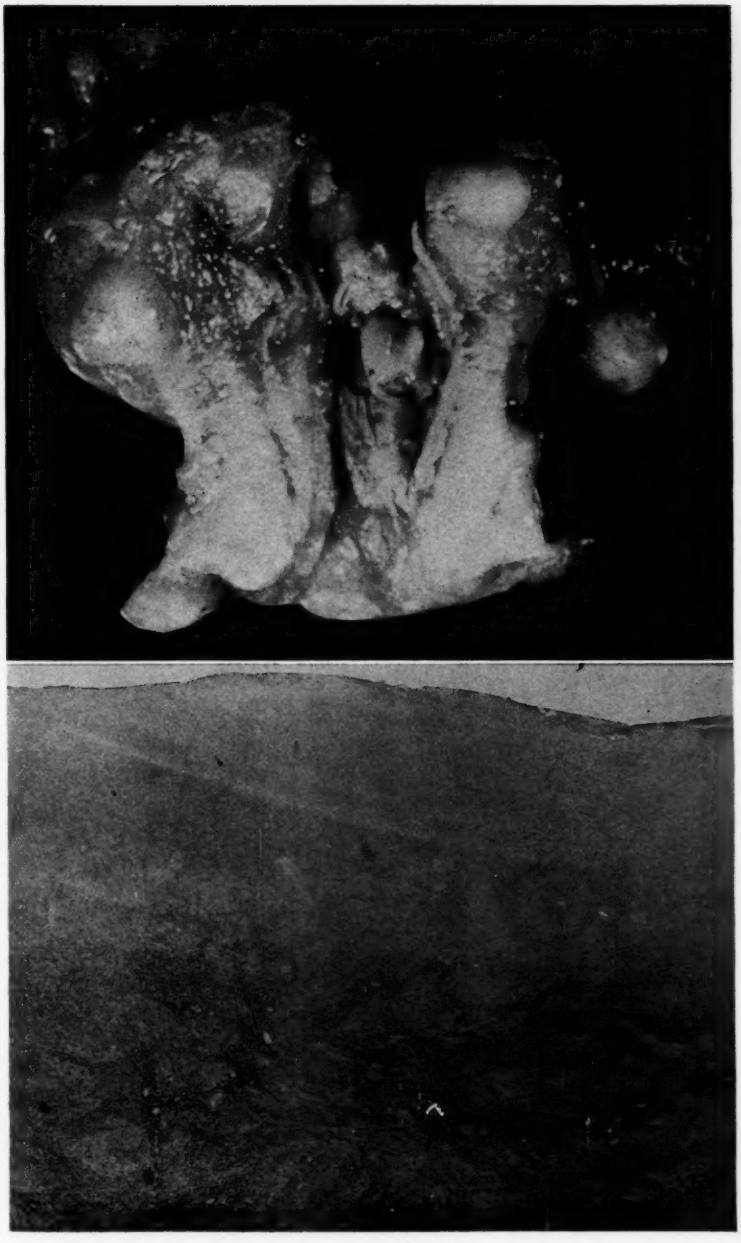

Fig. 6.

These divided the uterus into four segments, including the upper portion of the body, the lower portion of the body exclusive of the part adjacent to the internal os, and the portions of the body and the cervix immediately adjacent, and the remainder of the cervix (Fig. 5). Each of these four segments was

further divided by longitudinal incisions (in the long axis of the uterus) so placed that in blocks about 4 mm. in thickness all of the mucosa and as much as possible of the entire thickness of the wall were included. In the segments of the body of the uterus this was not feasible. Hence only the inner 1.8 cm. of the myometrium appeared in the blocks. Separate sections were made of the serosa and of the outer portion of the myometrium. The blocks were fixed in Bouin's fluid or in 4 per cent solution of formaldehyde. Paraffin sections from the surface of each block were prepared; then each block was cut approximately half way through and additional sections were made. Thus the entire endometrium and endocervix with the tissues adjacent were sectioned at intervals no greater than 2 mm. The preparations were stained with hematoxylin and eosin. When indicated, Verhoeff's elastic tissue stain and Masson's trichrome stain for connective tissue were utilized.

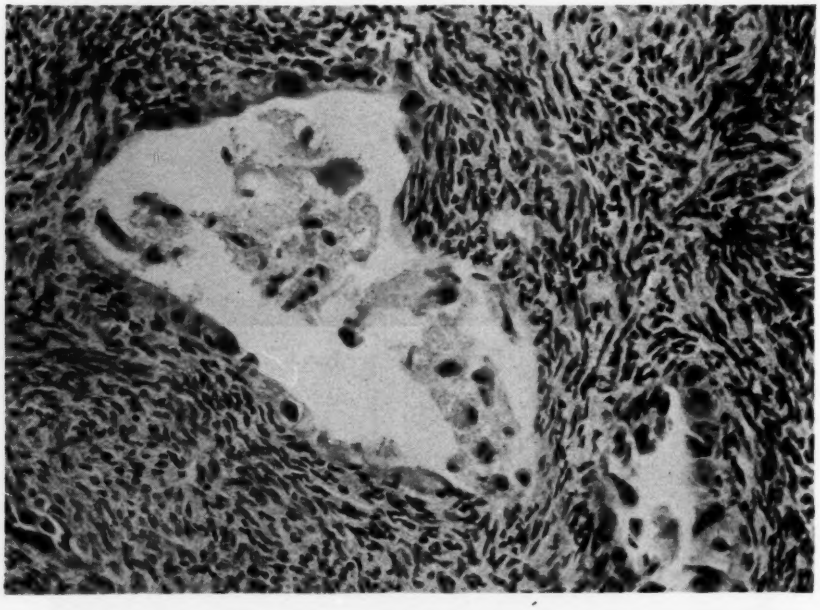

Fig. 7.

Radionecrotic Plaques

In all the cases the plaque was an irregular mass of partly soft and partly firm material. The size was variable from case to case, and the surface was elevated above the adjacent portions of the endometrium from which, in some cases, the plaque was well demarcated and could be lifted off; in others it was not. If no limits were apparent, the uterus was usually lined by necrotic material and the plaque was but a particularly thick portion of the necrotic lining. The plaque not only projected into the uterine cavity as much as 6 mm. but also extended into the adjacent myometrium as much as 5 mm. The base of the plaque was usually well demarcated from the adjacent myometrium.

Microscopic Structure.—

The plaque was an infarctlike surface zone of complete necrosis (Fig. 6). Beneath it lay a zone of partial hyalinization and edema and finally, between

this hyaline-edematous zone and the normal tissue, a zone of edema and possibly of atrophy. In the necrotic zone outlines of blood vessels can be traced and occasionally necrotic muscle bundles, depending on the depth of the plaque.

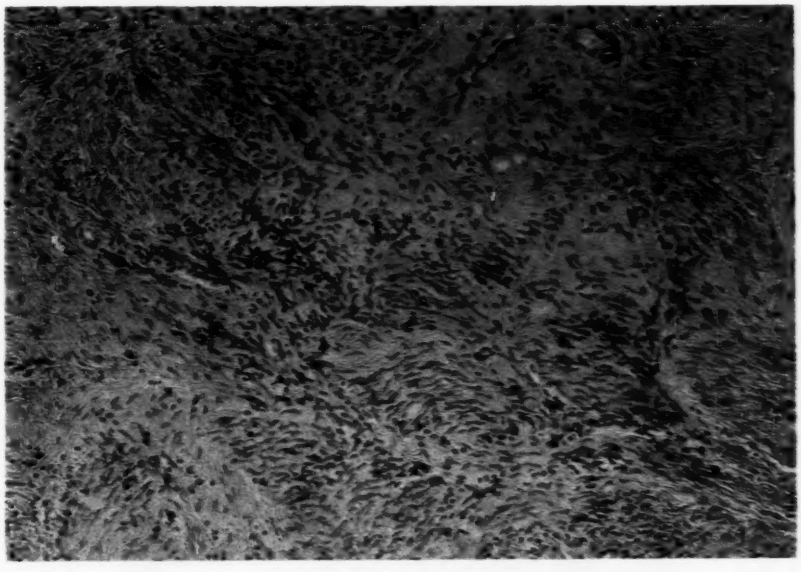

Fig. 8.

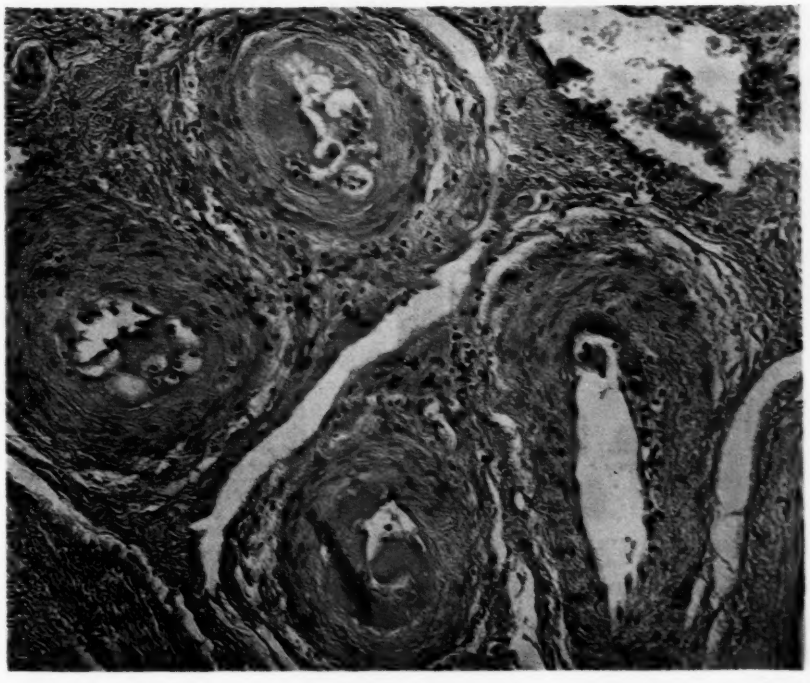

Fig. 9.

Endometrium: If present, the endometrium was atrophic, often mildly edematous and at least focally infiltrated by chronic inflammatory cells with deposition of fibrin and massive neutrophilic infiltration (Fig. 7). The stroma

of the deeper portions of the endometrium, around the bases of the glands, was edematous and infiltrated by lymphocytes, plasma cells, and monocytes, as well as by neutrophils. Epithelial cells of the endometrial glands (non-tumorous) showed marked radiation change.

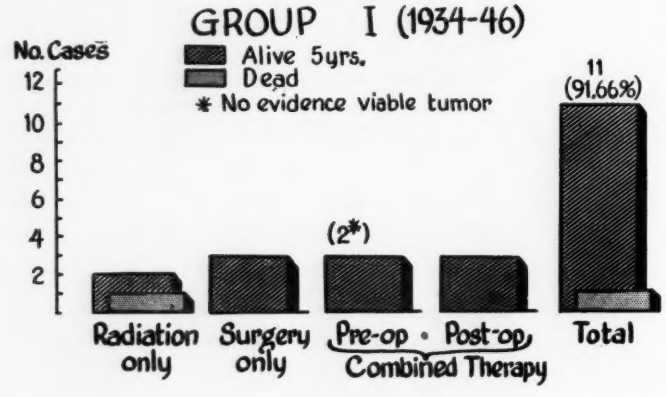

Fig. 10.

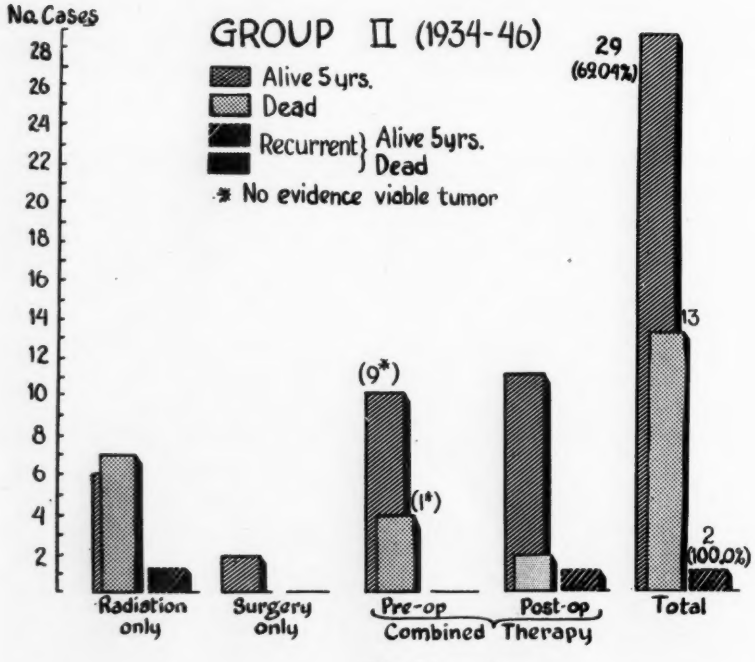

Fig. 11.

Myometrium: In none of the cases studied was a profound atrophy demonstrable and this is thought to be due to the fact that in all but a few instances the uteri were removed before these changes became evident. There was a definite diffuse increase in connective tissue between muscle bundles of the myometrium and individual muscle bundles appeared enlarged (Fig. 8). In the middle layer of the myometrium definite tissue swelling was seen in the walls of the arteries. No changes were seen in the serosal covering of the uterus.

In the hyaline-edematous zone and lower portion of the adjacent clot, fibrinoid necrosis of small vessels was apparent. In this and the adjacent edematous myometrial zone there were areas of only mild infiltration by lymphocytes,

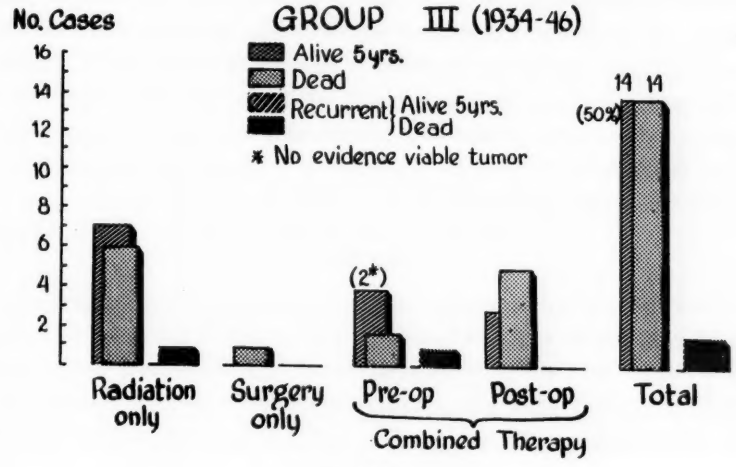

Fig. 12.

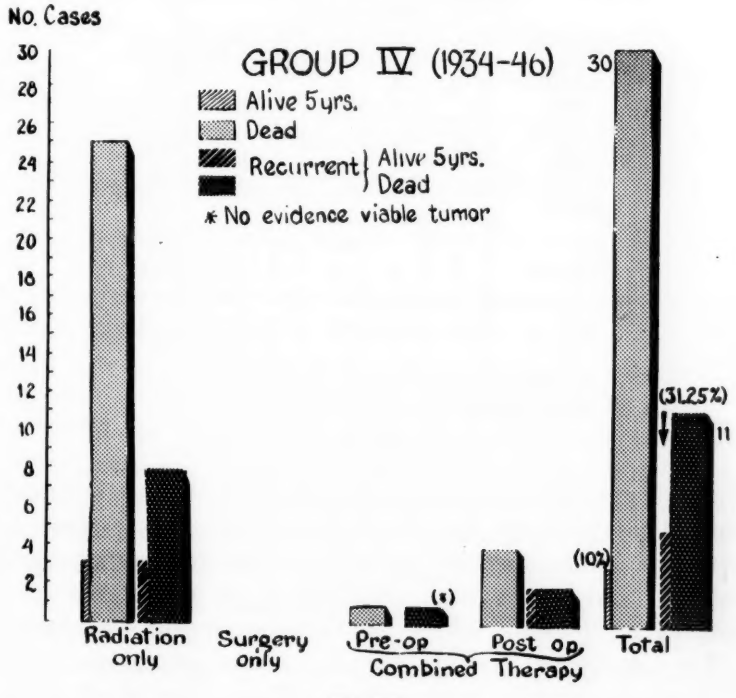

Fig. 13.

monocytes, neutrophils, plasma cells, and eosinophils. Elsewhere the infiltration by these cells was much more pronounced; and considerable hemosiderin, free or in macrophages, and numerous red cells were often intermixed. In the areas where a definite hyaline-edematous zone was in evidence, definite transitions from normal muscle fibers to thin atrophic muscle fibers to naked muscle

cell nuclei could be traced. As the stage of naked nuclei was approached there were increasingly larger deposits of hyalin around them. There is usually an accompanying marked chronic cervicitis.

Blood vessel changes: In the upper edematous, partially hyalinized myometrial zone and in the surface zone of complete necrosis with old hemorrhage, fibrinoid necrosis of small blood vessels occurred (Fig. 9). Deeper, even in the more normal myometrium but more often in or near the edematous myometrial zone, were a few hyalinized small arteries and also arteries with cells and fibrin or foam cell plaques in the intima. There was only a rare hyalinized arteriole near the endometrium.

Results

The material studied is comprised of two chronological groups. The first series of 140 cases was treated between the years 1934 and 1946 and may be considered in the light of five-year survival. The second series was observed between 1947 and 1951 and was studied primarily from a standpoint of irradiation effect, since sufficient time has not elapsed for evaluation in vital statistics.

ENDOMETRIAL CARCINOMA
1947–1951

GROUP	I	II	III	IV	NOT TREATED	TOTAL
Radiation only	–	8	3 1**	7 4**	–	18 5**
Surgery only	4	7	1	1	–	13
Pre-op.	6 5*	24 21*	2 1*	5 1* 2**	–	37 28* (75.76%) 2**
Post-op.	2	6	6 1**	4 1**	–	18 2**
Total	12	45	12	17	2	88

* No evidence viable tumor
** Recurrent

Fig. 14.

The effect of irradiation has been considered with regard to extent of disease, histological morphology, and irradiation dosage, since these factors have been suggested as influencing therapeutic results by Donovan and Warren,[2] Mahle,[6] Lindsay,[5] and others. In establishing the extent of the disease the clinical grouping of Schmitz, which we have previously described,[12] has been employed. The histological grading has consisted of an application of Broder's concepts of neoplastic activity with separate designation of adenoma malignum and adenoacanthoma. The adenocarcinomas have been graded from I to IV as follows: Grade I, well-differentiated, well-organized adenocarcinoma; Grade II, fairly well-differentiated, moderately rapid-growing adenocarcinoma; Grade III, rapid-growing, poorly differentiated adenocarcinoma with frequent medullary replacement of glandular elements; Grade IV, rapid-growing, poorly differentiated, predominately medullary-type adenocarcinoma. Finn[3] has lately

suggested a clinicopathological classification after an extensive review of numerous authors' attempts to clarify this problem. The distribution of gradings in our cases apparently strengthens his contention that the use of four histological grades is overrefined and that the purpose of histological classification might be served by the designations of well-differentiated, intermediate, and poorly differentiated, as suggested by Scheffey.[9] His exposition clearly reveals that the lack of uniformity in classification makes comparative studies difficult and cumbersome.

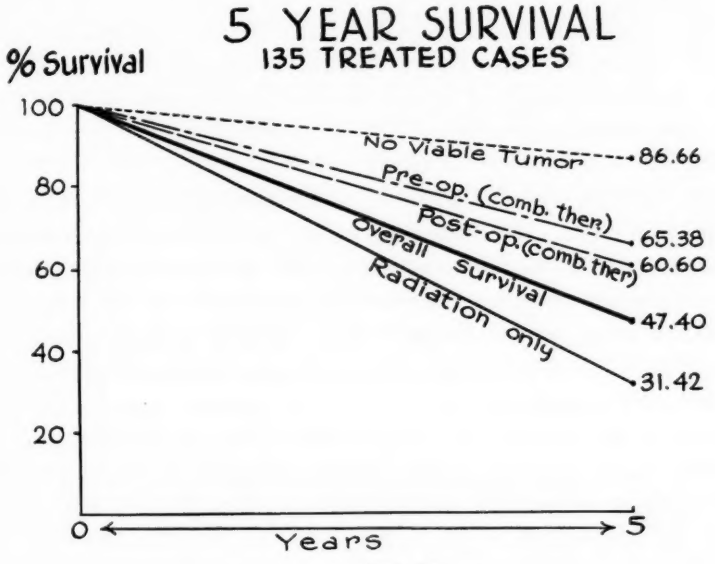

Fig. 15.

Figs. 10 to 14 present the over-all picture of the cases studied. In the first series, three cases were lost to follow-up, including the single case designated as dead in Group I. The other two cases were distributed in the fatalities of Groups III and IV, respectively. One other patient in Group III listed as dead succumbed to an ascending myelitis 41 months after treatment and no evidence of carcinoma was found on postmortem. The figures indicated by asterisks are those cases in which surgical specimens revealed no viable tumor by pathological examination. In Group II there was a single patient who died of cancer despite lack of evidence of tumor in the removed genitals. One year after operation, this patient developed an abdominal mass which was found to be omental metastases on exploratory laparotomy. She succumbed two years after her second course of x-ray therapy. The same situation obtained in the Group IV case, i.e., the removed genitals were determined to be free of disease after treatment but the malignancy was already established outside the pelvis. The cases listed as recurrent are those received at the Radiation Center, having been previously treated elsewhere and having developed recurrence after such treatment. Though of limited value statistically, the results in those latter cases demonstrate the potential salvage in adequate re-treatment of recurrent cases.

Since our preliminary report[14] we have been particularly interested in those patients subjected to genital extirpation after a course of radiation. At that time a detailed study was made of 11 cases, 6 of which showed residual carcinoma in the surgical specimen. In the years that have followed, we have been able to demonstrate an increasingly effective result in the eradication of active tumor by preoperative irradiation. This we ascribe primarily to a standardization of the preoperative radiation dose in the range of 6,000 mg. hr. of radium and a midpelvic dose of 4,000 R° to 6,000 R°. In the preliminary series it can be seen that of 26 patients treated with preoperative x-ray before the technique was established as routine, 15 cases (57.69 per cent) showed no evidence of viable tumor, irrespective of clinical grouping. In the later series (1947-1951) 35 patients received preoperative irradiation which generally corresponded to the standardized dose and 28 patients (75.67 per cent) in all groups were found to be free of active tumor.

Fig. 15 shows that the over-all survival of treated cases in the earlier series was 64, or 47.40 per cent. Combined therapy, both pre- and postoperative, was similarly successful, 65.38 per cent and 60.60 per cent, respectively. The survival rate in the cases showing no evidence of tumor in the combined preoperative groups, however, was 86.66 per cent. Radiation alone gave a salvage of but 31.42 per cent. The 6 surgical cases were too highly selected and few in number to be properly compared.

It is apparent, when considering the survival rate by groups, that the extent of the disease is a gravely influential factor. The large number of fatalities in Group IV treated by irradiation alone represent the many cases of extensive disease referred for palliative x-ray. We consider it an extremely hopeful sign that while the majority of cases were to be found in Groups III and IV in the earlier series, that situation is entirely reversed in the later series.

Histological grading bore no definite correlation to clinical extent of disease or survival. The majority of cases were classified as Grade II or III or intermediate grade of malignancy. It is of interest to note that the preoperatively treated cases included one adenoacanthoma which showed but little radiation effect in the removed specimen.

Comment

The various techniques for applying radium within the uterine cavity strive to obtain a fixed source which will produce a homogeneous irradiation of the endometrial cavity and entire uterus without overirradiating any single area. The difficulty encountered with most methods is due to the size of the uterine cavity which varies greatly and the distortion of the cavity by the new growth or complicating myomas. The multiple capsule packing method of the Radiumhemmet as adopted by Arneson[1] and Nolan[8] enjoys the widest usage because of the improved results obtained and the excellent dosage tables as published by Thoren,[16] and Nolan and Steele.[8] Although the latter authors studied the dose distribution in irregular uteri, they stated: "Irregularities in the size and shape of the uterus exert a general deleterious effect upon the effectiveness of multiple capsule implantations of radium for the treatment

of endometrial carcinoma. However, this effect is not so great for the multiple capsule method as it is with the tandem method of treatment.'' They further conclude: ''The results of treatment by this technique as described by Heyman and others indicate its superiority from a clinical standpoint.''

Study of the dose delivered from the Y capsule demonstrates an even distribution curve with the ability of the capsule to accommodate itself to the size of the cavity. By using divided dosage, much of the tumor, if proliferating, sloughs away in time to permit the arms of the capsule to lie in direct contact with the walls of the uterus at the second and third insertions. The finding of the necrotic plaque in every instance demonstrates clinically a radiation dose in the range of from 20,000 to 50,000 gamma roentgens to the endometrium, according to Nolan[8] who finds tumor control, with necrosis, in this range. This, we believe, is confirmed by our measurement of the dosage and the finding of destruction of the carcinoma in 75.67 per cent of uteri studied.

According to Miller,[7] ''The purpose of preoperative irradiation is to damage neoplastic cells to a point where manipulative spread at the time of surgery is unlikely.'' These and previous studies demonstrate complete destruction of the tumor in a high percentage of cases treated and changes in the glands, tumor cells, and blood vessels suggesting that such cells, if carried off through the blood stream or lymphatics, or dropped in the operative field, would have a difficult time surviving.

Although the number of cases treated by this technique before 1946 and available for study are few in number, we feel that certain facts are evident.

The over-all survival of treated cases before standardization of radium technique was 64, or 47.40 per cent. Combined therapy, both pre- and postoperative, was similarly successful, 65.38 per cent and 60.60 per cent, respectively. The survival rate in the cases showing no evidence of tumor in the combined preoperative groups, however, was 86.66 per cent. Radiation alone gave a salvage of but 31.24 per cent. It is apparent, when considering the survival rate by groups, that the extent of the disease is a gravely influential factor. Histological grading has no definite correlation to clinical extent of disease or survival. The majority of cases were classified as Grade II or III, or an intermediate grade of malignancy. The single case of adenoacanthoma which showed but little radiation effect in the removed specimen is of interest.

Conclusions

Endometrial carcinoma can be destroyed in 75.67 per cent of cases, with the use of the Y applicator of Schmitz to deliver 6,000 mg. hr. of radium within the uterine cavity, in addition to 4,000 r of 800 kv. x-ray delivered to the midpelvis.

Changes in the endometrium, myometrium, blood vessels, and tumor cells indicate that such therapy could retard spread of tumor cells, if still present.

It is possible to salvage 86.66 per cent of patients so treated and found to have no residual tumor.

The authors wish to express their thanks to Dr. John Sheehan, Director, and Dr. Vincent Mosquera, Associate, Department of Pathology, for their help in preparing and screening the multiple sections.

Our thanks are also extended to Dr. James Sandell, for the photography.

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Discussion

DR. A. N. ARNESON, St. Louis, Mo.—Dr. Schmitz's presentation brings into the foreground one of gynecology's modern controversies. Stimulus for use of preoperative irradiation in the treatment of endometrial cancer is, in large measure, due to the early work of Dr. Henry Schmitz and Dr. William Healy. In this country the procedure has attained some popularity, but few advocates are to be found abroad. Even after a substantial number of years the usefulness of preoperative irradiation presents, in the words of Dr. Novak, "a rather confused and fluid problem."

The mechanism by which the combined treatment may improve clinical results is vague. Attempts to study the question by comparing results following surgery alone with those obtained after preoperative irradiation are ineffective, due to uncertainties in uniformity in clinical material. The relation of such factors as histologic grade and uterine size to prognosis, and to control of tumor by irradiation, has been debated without definite conclusion. It has been established, however, that disappearance of tumor within the uterus is associated with a most favorable outlook.

Dr. Schmitz is eminently prepared to discuss this question by virtue of his years of experience, and the fact that his patients receive effective radium treatment by means of the "Y" applicator long used at his clinic. Destruction of tumor is attained in three-fourths of his patients, and the five-year survival in that group is 86.66 per cent. It is significant that he found no correlation between histologic grade and survival. Neither did microscopic appearance have a definite relation to extent of disease, but the stage of advance was found to be the most important factor in prognosis. His data are among the few that attempt to correlate extent of tumor with end results. The lack of a generally accepted classification for clinical stage has impeded evaluation upon that basis.

In our own experience we have not been able to demonstrate any clinical superiority for preoperative irradiation by comparing those results directly with values obtained after hysterectomy alone. That is largely due to the better prognosis prevailing in the latter group. Classification broadly made into differentiated and undifferentiated forms does, however, reveal for anaplasia a difference in survival according to method of treatment. Among 22 patients with undifferentiated cancer given preoperative irradiation, there are 13, or 59 per cent who are alive and well after five years. For hysterectomy alone the respective values are 5 of 16 patients, or 31 per cent.

It is not possible to show relationship between microscopic appearance of tumor and evidence of radiation control interpreted by examination of the removed uterus. There are 40 specimens, or 66 per cent, of the 60 irradiated preoperatively believed to show that phenomenon. For the differentiated lesions the result is 27/38, or 70 per cent, and in the undifferentiated 13/22, or 60 per cent. In close agreement with Dr. Schmitz's data is the survival of 35/40, or 87 per cent, of those showing disappearance of tumor, but only 7/20, or 35 per cent, with persistence.

In view of the importance tumor control within the uterus assumes in prognosis, it becomes essential to understand all factors contributing to that result. Tissue dose must be of considerable significance. There is evidence, without regard to the contribution from x-rays, that amounts in excess of 7,000 gamma are required if delivered over a period of three to ten days. The method of multiple radium treatments described by Dr. Schmitz is important in attempting to reach that level of dose, but a program of that order presents an economic dilemma as well as technical problems involved in attempting to avoid sequelae. Nevertheless, the usefulness of preoperative irradiation assumes therapeutic importance of considerable magnitude in the anaplastic lesion, the enlarged uterus, and in the more extensive tumor.

There is need for a standard classification for stage of advance in endometrial cancer. That classification should, ideally, take into account such data as might be obtained at curettement. We are inclined to pass lightly over that procedure, and limit our attention to removal of an amount of tissue adequate for examination.

Dr. Schmitz is to be congratulated for his contribution toward advance in the combined treatment of this disease, and in particular for his evaluation of results in relation to stage of advance.

DR. JOHN L. McKELVEY, Minneapolis, Minn.—It seems that my duty in regard to these malignant tumor problems is to act as advocatus diaboli. In 1938, the department of Obstetrics and Gynecology at the University of Minnesota Medical School set out to examine this question of the effectiveness of irradiation in adenocarcinoma of the endometrium. The histologic studies have been reported by Stowe, a preliminary clinical report published by McLennan, and a later report by me will appear shortly.

ADENOCARCINOMA OF THE ENDOMETRIUM (REPORTABLE)

	TOTAL NUMBER	SURGICAL RATE	ABSOLUTE 5-YEAR CURE RATE	TYPE OF TREATMENT ATTEMPTED
1928-1938		35.0%	42.5%	Large proportion treated with radium and x-ray
1939-1940	38	66.0%	58.0%	Attempt to treat as many as possible with x-ray, radium and panhysterectomy
1941-1946	116	67.0%	57.8%	Attempt to drop x-ray and treat as many as possible with radium and panhysterectomy
1947-1949	37	86.5%	*68.0%	Attempt to drop x-ray and radium and treat as many as possible with panhysterectomy

*Calculated survival rate using 1939-1946 experience of relation between two-year survival and five-year cure and applying it to 1947-1949 two-year survival rate.

In order to avoid the error which is introduced by the automatic selection inherent in the application of a given form of therapy, the end results in terms of absolute five-year cures for the total reportable material treated over a given time period were used as the test of the effectiveness of a given therapeutic attack. The material seen between 1928 and 1938 was used as a control. This showed a 35 per cent surgical rate (simple panhysterectomy and bilateral salpingo-oophorectomy). Most of these had added radium and/or x-ray and the remainder were for the most part treated with irradiation of one sort or another alone. The details of this therapy are given in McLennan's publication. Beginning in 1939 an attempt was made to treat as many patients as possible with x-ray, radium, and surgery as above until a series was accumulated. The x-ray was then withdrawn and an attempt made

to apply radium and surgery as widely as possible. Finally, in the most recent series, the radium was dropped and surgery alone applied with an attempt still further to increase its rate of applicability. An insufficient number of this last group has passed five years since treatment to be significant. Calculations based on the two-year survivals in this group as compared with the relation between the two-year and five-year survivals of the previous groups are presented for what they may be worth.

There seems to be evidence from this material that the surgical rate can be increased and will produce an increase in the five-year cure rate. There is no evidence that withdrawal of x-ray therapy adversely affected the cure rate. There is no evidence that withdrawal of radium adversely affected the cure rate although this conclusion must wait for a demonstration of the reality of the calculation of the survival for the last group.

These data suggest that the surgical rate is the most important factor in determining the cure rate for the group. Whether routine irradiation in one form or another will have an effect upon the frequency of vaginal metastases or vaginal wound implant does not appear to be proved. There is no evidence of it in our material but such an effect could well be hidden by the effects of the increasing surgical rate if the change were not great.

One must object very strongly to drawing conclusions as to the value of a given form of therapy from a selected group of patients. Selection may be voluntary but it is often involuntary as well. In our experience, not all patients will tolerate, for example, x-ray, radium, and surgical therapy. Those who do are automatically selected for a variety of things. If one wants a real answer to the effectiveness of these agents, he should attempt to apply them as widely as possible to a total material and then compare the results with a subsequent similar material treated as widely as possible with another form of therapy such, for example, as surgery alone.

The study of the therapy of adenocarcinoma of the endometrium is far from finished. Planned studies are required. The overwhelming significance of the surgical rate which has impressed us may not tell the whole story but it does appear to be the major factor involved.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I think Dr. Schmitz and Dr. McKelvey have pointed out avenues of investigation which are vitally important. On the other hand, there is a certain significance from clinical evaluation that cannot be discounted. I would like to show comparative tables that explain why we have been supporters of preoperative irradiation therapy (slide information to be inserted here) whenever possible, prior to hysterectomy and bilateral salpingo-oophorectomy without nodal dissection or postoperative irradiation, and without surgical mortality.

TABLE I. CARCINOMA OF THE CORPUS, FIVE-YEAR RESULTS, 1921-1946

TREATMENT	PATIENTS	SURVIVAL	PERCENTAGE
Adequate surgery only	16	10	62.5
Adequate or inadequate surgery with or without irradiation (unplanned)	44	21	47.7
Radium only	31	17	54.8
X-ray only	2	0	0.0
Radium and x-ray	38	17	44.7
Preliminary radium plus adequate surgery. No postoperative x-ray (planned technique)	46	42	91.3
Total	177	107	60.4 (rel.)

Follow-up, 100 Per Cent
Over-all Operability Rate, 60 Per Cent

TABLE II. CARCINOMA OF THE CORPUS (PLANNED TECHNIQUE) FOUR- AND THREE-YEAR TRENDS, 1946-1951

TREND	PATIENTS	SURVIVAL	PERCENTAGE
Four-year	12	11	91.6
Three-year	9	8	88.8

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—Dr. Schmitz is to be congratulated on this valuable contribution which demonstrates that a greater rate of survival is attained by complete destruction of the tumor by radiation before operation. If we did not believe this we would not use it, would we? Unfortunately, none of us has enough material of his own to be significant statistically. Dr. Craig W. Muckle reviewed some of the recent literature on this subject and came up with the following figures:

1,794 patients were treated by surgery alone with a survival rate of 56.8 per cent.
460 patients with combined treatment (preoperative irradiation by intrauterine application of radium or x-ray) had a survival rate of 70.4 per cent.

This is a difference of 13 percentage points and an actual difference of about 20 per cent. To me this means that we are saving one additional patient out of every five by utilization of preoperative irradiation.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I have a couple of tables to show which I believe corroborate what Dr. Schmitz has said about the value of preoperative radiation for carcinoma of the endometrium. These two tables represent cases that were managed personally by myself. Although the groups are small, the statistics are very characteristic.

TABLE I. CARCINOMA OF ENDOMETRIUM. HYSTERECTOMY WITH POSTOPERATIVE RADIATION

NUMBER OF CASES	SIX OR MORE YEAR SURVIVAL	DEATH FROM RECURRENCE	PER CENT SURVIVAL
14	8	6	57.1

These are patients treated years ago before we began to use preoperative radiation. The diagnosis was made by curettage and in case carcinoma was found, hysterectomy was performed a few days later. As the table indicates, the survivals of five years or more represent 57.1 per cent.

TABLE II. CARCINOMA OF UTERINE FUNDUS. TREATMENT BY HYSTERECTOMY WITH PREOPERATIVE AND POSTOPERATIVE SUPERVOLTAGE ROENTGEN THERAPY

HISTOLOGIC GRADE	NUMBER OF CASES	5 PLUS YEARS' SURVIVAL	PER CENT SURVIVALS
I	12	12	100.0
II	14	12	85.7
III	2	1	50.0
IV	1	0	0.0
All grades	29	25	86.1

These are also patients managed personally by myself. Each patient was radiated preoperatively with radium and supervoltage roentgen therapy, and after the hysterectomy performed six or eight weeks later, the roentgen therapy was repeated. The roentgen therapy is managed by the Department of Roentgen Therapy and the apparatus used is a 600,000 volt (constant) machine. In this series we have a five-year survival of 86.1 per cent.

I am somewhat surprised that Dr. Schmitz does not feel that histologic grading affects the survival results. We are willing to agree that the clinical stage of the disease is very important. Our pathologist is not eager to assign grades of malignancy by number, but he does ascribe a greater degree of malignancy to some than to others.

It will be noted that we list 100 per cent survivals in Grade I, and 85.7 per cent in Grade II, with fewer survivals in Grades III and IV. We believe the over-all results will depend upon how great a number of the less malignant grades are in a series. For that reason a larger series is more likely to be accurate.

The over-all results obtained at Harper Hospital by the entire staff in a somewhat larger series show 47.8 per cent survival following hysterectomy and postoperative radiation, while with both pre- and postoperative radiation the five-year survivals represent 81.2 per cent.

We at Harper Hospital believe that preoperative radiation definitely raises the percentage of survivals.

DR. SCHMITZ (Closing).—Dr. Arneson and Dr. Kamperman brought up the question of histologic grading of the tumors and the clinical extent of the tumor. I believe this is due to the fact that if you are treating a localized tumor within the endometrium or one with very little infiltration into the myometrium, with a dosage capable of producing radiation necrosis and destruction of the tumor, which dose Nolan estimates must be between 20,000 and 50,000 gamma r, then you destroy the tumor irrespective of its grade.

The question Dr. McKelvey proposes I answer in my mind by two observations. First, in our own series and in other comparable series reported, the operability has increased year after year. In his first group studies with an operability rate of 35 per cent and in the later group with, I believe, an operability rate of 89 per cent, we are dealing with many patients with an earlier stage of the disease and, therefore, those series cannot be compared unless Dr. McKelvey has broken his patients down into a clinical classification so that he can tell us that in the first group studied the Grade I tumors gave the same results as in the second and third series with similar extent of disease and histologic type. The second observation is the improved surgical technique in all our clinics. To my knowledge, Dr. McKelvey has given no consideration to the fact that in all probability the surgical removal of the uterus today is more thorough than it was when he first came to Minneapolis.

Dr. Kamperman shows a marked difference in his survival rates and I have a great deal of respect for his radiologist; he shows 47 per cent survival with postoperative radiation and 81.2 per cent in the preoperative, plus postoperative, radiation group.

Dr. Scheffey's work in the malignancies has been outstanding. In my discussion in the paper I have, of course, given recognition to the work of Drs. Healy, Arneson, Scheffey, and Norris who have contributed so much to the study of this type of cancer. I feel we have made a great deal of progress.

THE EMPIRIC USAGE OF LOW-DOSAGE IRRADIATION IN AMENORRHEA*

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(From the Department of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, and the Albert Einstein Medical Center)

THE avoidance by most gynecologists of low-dosage irradiation therapy in the face of the favorable clinical reports published during the past twenty-five years is based, as Collins[1] recently ascertained, on two major objections. The first of these is the illogicality of employing a modality of unknown action, and the second is the fear of injury to germ plasm. These stumbling blocks of rationalization must be hurdled by anyone who chooses to use the method.

The Mode of Action of Low-Dosage Irradiation

Despite wide interest in and frequent use of low-dosage roentgen therapy in the management of dysfunctional menstrual disorders for many years, the mechanism by which x-rays effect changes in function of the pituitary and ovaries is unknown. Since the basic effects of radiation depend on alteration of intracellular metabolism and chemistry, the key to understanding the problem lies in comprehending how a cell lives and functions, a mystery still to be unraveled. The manifold explanations of its action, although provocative, constitute so much philosophic abracadabra. The many theories proposed can be divided into those referring to "stimulation" and those alluding to selective "destructive" action. Aherents[2-4] of the theory of stimulative action believe that small roentgen doses increase glandular function by means of either alteration of biochemical factors, including changes in cell permeability and rearrangement of electrons, atoms, and molecules, or through production of active hyperemia which results in increased metabolic activity. On the other hand, numerous others[5-7] prefer to believe that the apparent stimulation of function following low-dosage therapy occurs through removal of some inhibitory influence on normal glandular activity. In the ovary, the latter theory implies destruction of large follicles or of a persistent corpus luteum, the presence of which may be preventing growth and maturation of additional primordial follicles. Many attempts have been made to determine experimentally which of these two major theories is correct.

The number of animals, including mice, rats, cats, dogs, rabbits, and monkeys, which have been subjected to doses of irradiation comparable to those employed in the human being is legion. When the experimental x-ray dosage is scaled down to the size of the animal in relation to the size of the human being, no cytological changes are observed in either pituitary[8, 9] or

*Presented, by invitation, at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

ovaries.[10] Moreover, it has been shown that the irradiated pituitary continues to function normally,[11] and that the ovaries remain responsive to gonadotrophin.[12] The theories of the mode of action of small roentgen doses, despite various opinions crystallized from experiments, remain widely divergent and contradictory. Failure to demonstrate morphologic changes in animals subjected to low-dosage irradiation has not deterred search for such changes in man. When such observations have been made, no histologically demonstrable changes were noted.[13] It is therefore impossible, at this time, to ascribe the effects of low-dosage irradiation therapy to any known anatomic change. Demonstration, however, that such treatment is capable of "waking up" a hypofunctioning gland to the point of causing changes in hormonal assays would be valuable evidence of functional alteration in the irradiated gland. Rakoff's[14] studies in 12 anovulatory sterile women who had been subjected to low-dosage irradiation revealed significant favorable changes in the endocrine status of each of the 7 patients who improved clinically. The simultaneous increase in urinary excretion of both gonadotrophin and estrogen, which occurred in these 7 patients, was rapid, appearing occasionally during the two weeks of the therapy period but usually within a month of beginning treatment. More recent observations of Rakoff[15] indicate that irradiating only the ovaries of patients with primary ovarian deficiency is followed by a fall in gonadotrophin excretion and a simultaneous rise in estrogen excretion, suggesting that ovarian irradiation is functionally specific and that pituitary irradiation may be omitted in such patients.

Possible Genetic Effects

Ever since 1927, when Muller[16] showed that the natural rate of appearance of new mutations could be increased in *Drosophila melanogaster* by means of x-rays, much speculation has occurred with regard to the applicability of these observations to man. A large body of data has been accumulated dealing with the relation of mutation frequency to acute and chronic irradiation in plants, such as corn, barley, and beans, and in mammalian forms. Since there is no question concerning the ability of x-rays, radium, and other radioactive substances to modify germ plasm in high dosages, the challenge is to recognize that dosage which is genetically harmless. Radiation geneticists are generally agreed that mutation frequency bears a direct relation to high total dosage of irradiation. They are not, however, agreed that the linear relation of the mutation-induction rate per roentgen pertains to low dosage. The dosage of x-rays employed to study the genetic effect of irradiation in plants and animals is many times that used in low-dosage irradiation therapy. Muller's[17] experiments on the fruit fly were made with high-dosage x-rays; he administered 150 r to the entire fly, a quantity equal to that employed in treatment of menstrual disorders. Similarly, in the experiments of Little and Bagg,[18] brown mice of well-known stock were given one-fifth of a human erythema dose to the entire dorsal surface on each of 5 successive days. The second and third generation descendants of the irradiated animals showed ab-

normalities of all the feet. However, the quantity of irradiation to which these mice were exposed, one-fifth of a human erythema dose, is more than twice the one-twelfth of an erythema dose employed in low-dosage therapy.

Recent studies have shown that, despite the linear relation of mutation rate to large-dosage radiation, small doses do not have a notable effect on the genetic inheritance of descendants. No conclusive evidence for production of either visible or remote genetic changes during six generations was obtained by Lorenz and associates[19] in mice permitted to breed while subjected continuously (during 24 hours) to 1.1 r daily. Although there is no threshold below which irradiation fails to induce mutations in the fruit fly, there is reason to believe that *extremely* low doses do not increase noticeably the expected mutation-induction rate.[20] Spencer and Stern[21] showed that a dose of 50 r administered to *Drosophila melanogaster* in the same fashion as Muller's 150 r doubles the control (natural) rate of mutations but that a dose of 25 r results in a mutation rate but slightly more than the control rate, suggesting that the lowered dosage does not alter the genic inheritance of later generations. From these and other observations,[22-24] it seems possible that genetic effects per roentgen are negligible for small roentgen quantities, and not at all comparable to the damaging effects known to follow higher x-ray dosage. If this is true in man, as it appears to be in animals, the stricture of Muller concerning the danger to future generations from application of x-rays to ovaries does not apply to the dosage employed in the type of treatment under discussion.

There is, in addition to dosage differences, another important limitation in drawing a parallel between experimental studies and possible effects of similar irradiation in man. This is imposed by the necessity of irradiating the whole body of some animals, a procedure followed by "a complicated sequence of changes which are more or less interrelated and interdependent" (Ingram[22]). It is impossible to compare with accuracy the effects of whole-body irradiation, as pertains in either fruit fly or smaller rodent, with those observed both in human therapy and in experiments employing larger species, wherein specific organ areas are irradiated. "There is something in a total body irradiation which causes greater damage to a particular organ than localized irradiation at a much higher dosage" (Bloom[25]). This was shown in the studies of Lorenz and associates[19] who demonstrated that merely 300 r of whole-body irradiation in mice resulted in permanent sterilization but that it required 700 r administered locally to the ovaries to obtain the same result. The injurious effects of experimental total-body irradiation are evident also from the changes observed in adrenal cortex function.[26] The fact that most of the experiments universally cited for the mutation-rate effects in animals involve total-body exposure, as well as the fact that large experimental dosages cannot be collated with low-dosage therapy, suggests that the genetic dangers of such therapy have been overemphasized and indicate that the attitude of alarm may be safely discarded. This must not be construed to mean that there is no hazard. It is clear from the direct linear relation of radiation dosage to the genetic disasters described in preceding paragraphs that low dosage must be carefully maintained. Such

caution applies to any type of pelvic area irradiation, including serial-type diagnostic roentgenograms. Even though the quantities of penetrating x-rays employed in diagnostic procedures are small, frequently repeated exposures may be cumulatively significant.[27]

Present Report

This presentation is concerned with the empiric use of low-dosage irradiation in secondary amenorrhea and is composed of an analysis of 124 patients treated during the fifteen-year period, 1936 through 1950, in the author's practice. The decision to review experiences drawn only from private practice was based on the belief that closer scrutiny would result because of personal knowledge of each patient's history and course. In addition to tabulation of results, this report comprises a marshalling of the indications, contraindications, and the technique of low-dosage irradiation as applied to this group of patients.

Indications

The current study includes no patient with primary amenorrhea, hypomenorrhea, or sterility associated with regular menstruation.

The indication for low-dosage roentgen therapy in each patient of this series was secondary amenorrhea, a term indicating that the patient had previously experienced some type of menstrual cycle. Such dysfunctional secondary amenorrhea may be of short or long duration. For clinical purposes, it is our custom to employ the term "amenorrhea" when the interval between periods is four or more months and to use the expression "oligomenorrhea" when the menstrual intervals are less than four months.

The etiology of these two variants of the unphysiologic absence of menstruation, while undoubtedly similar, is not past dispute. In spite of the wealth of information furnished by the investigations of anatomists, physiologists, and chemists, a clear understanding of oligo- and amenorrhea is still lacking and there is no universally acceptable, simple, uniform method of treating them. Such a menstrual disorder is essentially a symptom of either local or constitutional derangement which may or may not be endocrine in character. It is expedient to side-step the complexity of the problem by regarding the symptom of amenorrhea as an entity. Of itself, the absence of menstruation is relatively unimportant unless the patient is desirous of having offspring. On the other hand, it must be presumed that such offspring is, or will be, desired by any young woman, married or as yet unmarried. Amenorrhea, from such a standpoint, assumes importance; its continued presence may lead to irreversible atrophy of the uterus, a serious impediment to reproductive function. Of greater significance, though not sufficiently emphasized, is the fact that women who conceive despite the presence of a menstrual disorder have faulty reproductive careers.[28, 29] It is therefore essential, in the interest of obviating pregnancy wastage, to recognize the value of preconceptional therapy of amenorrhea.

The proper approach to treatment of amenorrhea embodies thorough understanding of the chain of organs involved in the mechanism of normal men-

struation, namely, the anterior hypophysis, ovaries, uterus, and the two associated endocrine glands, thyroid and adrenals. By assaying for pituitary gonadotrophin, one is able to determine whether or not the basic disorder lies within the ovary or within the pituitary gland. It is not, however, always possible to follow such a rational course. For practical purposes, it is often necessary to determine merely responsiveness of the endometrium and to treat amenorrhea in an empiric fashion, regarding its presence as an indication for low-dosage irradiation therapy of the pituitary gland and ovaries. Under such circumstances, it is imperative to recall the contraindications to this treatment.

Contraindications

The following conditions are regarded as contraindications to the x-ray treatment:

1. Previous Unilateral Oophorectomy.—The appearance of amenorrhea in a woman previously subjected to unilateral oophorectomy is a harbinger of failing ovarian function. The factors governing such failure are unknown but the amenorrhea, irrespective of treatment administered, is likely to be progressive. If the latter should occur following low-dosage irradiation, the therapy would be unfairly condemned.

2. Immature Ovaries.—Inception and maintenance of menstrual cycles are governed by establishment and continuous integrity of the pituitary-ovarian-uterine mechanism. However, during puberty, before that mechanism is well established, the length of the menstrual cycle is extremely variable. Its irregularity is such that periods of amenorrhea are looked upon as being normal in adolescent girls. Since physiologic development of the ovaries is not fixed in point of time, amenorrhea of adolescence requires no treatment beyond measures to improve nutrition and to channel the emotional storms of these eventful years. Low-dosage irradiation should not be administered to girls under the age of 20 because it is not possible to define the degree of secondary amenorrhea until that time.

3. The Possibility of Early Pregnancy.—There is no evidence to indicate that preconceptional pelvic irradiation has any deleterious effect upon children subsequently conceived.[30, 31] The dangers to the embryo of postconceptional pelvic irradiation within therapeutic range are, however, well known. During the first trimester of pregnancy, death of the fetus and abortion usually follow exposure of the pelvic area to 2,000 r in divided doses during a three-week period.[32] A lesser quantity of heavy pelvic irradiation administered during early pregnancy is likely to result in malformed children, though some may be normal.[33, 34] While ordinary diagnostic roentgen procedures employing dosages far less than the therapeutic range do not usually damage the early embryo, a large number of repeated photographic exposures may be detrimental.[27, 35] In general, the incidence and severity of fetal damage are proportionate to both the dosage of radiation and the immaturity of the exposed embryo. Reviewing this subject with great clarity, Miller, Corscaden, and Harrar[34] state: "It seems reasonable to advise that the use of

radium and x-ray during pregnancy for treatment purposes be restricted to very clear and urgent indications, and that the use of diagnostic x-ray examinations be not too frequently repeated during pregnancy. . . . It seems advisable to interrupt any pregnancy which has been subjected to therapeutic radiation, for it is generally admitted that serious radiation effects on the offspring will result in a high percentage of cases."

In view of our lack of knowledge of the precise quantity of irradiation which is harmful to the fetus, it is best that no therapeutic radiation, however minimal, be permitted during early gestation. The recent report[36] of the birth of a normal child following the unknowing use of low-dosage irradiation to the ovaries at the inception of pregnancy is not sufficiently reassuring to warrant freedom from fear of the effects of such irradiation on a developing embryo. Low-dosage irradiation should never be instituted during a period of amenorrhea without certainty concerning the absence of pregnancy, irrespective of the patient's history of prior barrenness. This opinion is supported by the experience of one of the patients cited below. If the secondary amenorrhea is mild, the intervals being from two to four months (oligomenorrhea), roentgen therapy is withheld until the patient has one of her menstrual episodes. If the secondary amenorrhea is severe, the intervals being more than four months, treatment is not started until uterine bleeding is evoked by means of steroidal administration and withdrawal. In both instances, even though low-dosage therapy is initiated immediately following menstruation—spontaneous or induced—it is imperative that pregnancy not occur during the two weeks which elapse before completion of the three required treatments. The patient, informed clearly of the importance of avoiding pregnancy temporarily, must be emphatically instructed either to avoid intercourse or to employ contraceptive measures during the brief treatment phase.

Technique

Low-dosage irradiation was administered to the 124 patients according to a calibrated modification of the early Edeiken[37] method. The treatments were administered to 101 of the 124 patients by a single radiologist,* the remaining 23 being treated by two other radiologists. Both pituitary and ovaries were irradiated at each of the three sittings, one week apart. The pituitary gland was irradiated through a lateral portal of 3 by 3 cm., the central ray passing through the midpoint of an imaginary line joining the outer canthus of the eye and the external auditory meatus, the sides being alternated weekly. A single anterior portal of 15 by 15 cm. was employed for ovarian irradiation, the lower border of the field being centered just above the symphysis pubis. (No attempt was made, as in the slightly higher dosage technique of Kaplan,[31] to irradiate each ovary separately.) The factors employed were 140 kilovolts, 50 cm. focal skin distance, and filtration of 0.25 mm. of copper plus 1.0 mm. of aluminum. A dose of from 80 to 100 r, measured in air, was given each week to each field. The total dose reaching the

*Dr. Edward Dessen.

pituitary and ovaries in women of average size is approximately equal since the pituitary gland is about the same distance from the outer canthus (8 cm.) as the ovaries are from the anterior abdominal wall. It may be calculated from depth-dosage tables that less than half of the dosage administered, namely, 35 r, is delivered at a depth of 8 cm.[38] Thus, the total dosage received by the pituitary and by the ovaries from three treatments approximates 105 r, the former receiving slightly less because of differences in backscattering. Such a small quantity of x-rays, while not comparable to the lesser dosage of diagnostic studies, rarely causes untoward gastrointestinal reactions. An occasional patient does, however, complain of nausea during the course of therapy.

Patients Omitted From Analysis

Thirty-four of the 124 patients could not be included in the final analysis of therapeutic results for one of the following reasons (Table I):

1. Failure to complete prescribed course: Four patients did not take the full dosage of irradiation, electing rather to discontinue therapy after one or two treatments.

2. Incomplete follow-up: The possibility of temporary spontaneous improvement is a snare to which the overzealous and the not too critical may be a prey in evaluating therapy in dysfunctional menstrual disorders. With the hope of avoiding such a pitfall, no patient was included in the final analysis of this series unless her menstrual cycle had been followed for one year after treatment. This caused elimination of 10 of the 124 patients.

3. Antecedent adjunctive therapy: It is well recognized that mild menstrual disorders may be benefited by such measures as cervical dilatation (as part of the technique of uterine curettage) and cyclical steroidal therapy. If either of these measures had been employed in any patient less than three months prior to x-ray therapy, the result was not included. This precluded analysis of results in 20 patients.

TABLE I. REASONS FOR OMISSION OF 34 PATIENTS FROM FINAL ANALYSIS OF RESULTS OF LOW-DOSAGE IRRADIATION IN 124 AMENORRHEAL WOMEN

REASONS FOR OMISSION	NO. OF PATIENTS
Incomplete course of therapy	4
Follow-up less than one year	10
Too recent adjunctive treatment	20
Total	34

Analysis of Results

After deliberate omission of 34 patients from the series of 124 for reasons described in the preceding paragraphs, 90 amenorrheal patients remained for analysis. The criteria for evaluation of results were somewhat didactically chosen as follows:

1. "Cure" of secondary amenorrhea was considered to have taken place if menstruation was regularly cyclic for one year following treatment. If periods were cyclic and pregnancy occurred prior to the end of a year, the

patient was considered to have satisfied the criteria of cure even though subsequent menstrual regularity could be ascribed, with propriety, to the gestation. The appearance of regular cycles more than eight weeks following the last x-ray treatment was considered fortuitous, and not a therapeutic result.

2. "Improved" patients were those whose menstrual intervals were reduced to at least one-half of their pretreatment length.

3. The therapy was considered a "failure" in those patients whose menstrual intervals were not diminished within three months of the final x-ray treatment.

Viewed according to these criteria, the 90 patients treated by means of low-dosage irradiation for secondary amenorrhea were found to have attained an over-all cure rate of 71.1 per cent (Table II). The response of the 90 patients to x-ray therapy was analyzed according to age, duration of the amenorrhea, and nature of the menstrual flow immediately preceding the irradiation. In addition, it seemed desirable to review the pregnancies which followed soon after therapy and, finally, to particularize the single deleterious result.

TABLE II. RESULTS OF LOW-DOSAGE IRRADIATION IN 90 WOMEN WITH SECONDARY AMENORRHEA

RESULT	NO. OF PATIENTS	PERCENTAGE
Cure	64	71.1
Improved	5	5.6
Failure	21	23.3
Total	90	100.0

Age of Patient.—The age of the 90 patients ranged from 20 to 35 years. Inasmuch as the primary reason for employing low-dosage irradiation in secondary amenorrhea is not merely to regulate menses but rather to improve fertility, either immediate or remote, the treatment is not applicable to women beyond the age of 35 years. It is likewise not administered, for the reasons mentioned previously, to adolescent girls. Since the age differential in regard to ovarian function from 20 to 35 years is not great, it might have been anticipated that little difference in results would be noted at the varied age levels of the 90 patients. The positive pattern of response approximated 70 per cent in each age grouping (Table III).

TABLE III. CONSTANCY OF RESPONSE OF 90 AMENORRHEAL WOMEN OF VARIED AGE TO LOW-DOSAGE IRRADIATION

AGE (YEARS)	NO. OF PATIENTS	CURED	
		PERCENTAGE	NUMBER
20-24	48	34	70.8
25-29	25	17	68.0
30-35	17	12	70.6

Duration of Amenorrhea.—It has been the uniform experience of others that the favorable results following radiation therapy vary inversely with the degree of amenorrhea—the greater the interval between periods, the less the

response to low-dosage irradiation. As may be seen from Table IV, the 90 patients were not exceptional in that regard. It is, however, apparent that the series is numerically weighted in favor of oligomenorrhea which was treated twice as frequently as amenorrhea (61:29). The results attained in the two groups are not, therefore, statistically comparable. It is, nevertheless, significant that the amenorrheal patients who failed to menstruate regularly after irradiation were those who had the longest periods of amenorrhea. Of 24 patients whose menstrual interval was between four and twelve months, 15 responded favorably to treatment. On the other hand, 5 of those whose amenorrhea was of two or more years' duration failed to improve (Table V).

TABLE IV. COMPARISON OF RESULTS OF LOW-DOSAGE IRRADIATION IN OLIGOMENORRHEA AND AMENORRHEA

RESULT	NO. OF PATIENTS	OLIGOMENORRHEA		AMENORRHEA	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Cure	64	49	80.3	15	51.8
Improved	5	2	3.3	3	10.3
Failure	21	10	16.4	11	37.9
Total	90	61		29	

TABLE V. VARIATION IN RESULTS OF LOW-DOSAGE IRRADIATION IN AMENORRHEAL WOMEN IN RELATION TO LENGTH OF MENSTRUAL INTERVAL

MENSTRUAL INTERVAL (MONTHS)	NO. OF PATIENTS	RESULT					
		CURE		IMPROVED		FAILURE	
		NO.	%	NO.	%	NO.	%
4-12	24	15	62.5	3	12.5	6	25.0
24 or more	5					5	100.0

Pretreatment Menstruation.—The necessity of excluding the presence of pregnancy prior to initiation of low-dosage therapy is, as has been stressed previously, obligatory. The plan of treatment is to have the patient begin the roentgen series at the conclusion of a menstrual flow, a plan which, in addition to affirming the absence of pregnancy, assures the presence of currently responsive endometrium. If the patient has oligomenorrhea, it is expedient to await the appearance of a spontaneous period. If the patient has amenorrhea (intervals of more than four months), uterine bleeding may be induced by means of either estrogen alone or estrogen and progesterone, the manner of its induction being irrelevant. Appearance of a single period following prefatory steroidal therapy should not be considered as an important contribution to regulation of the menses, except as it indicates aptitude of the endometrium to react to ovarian hormones. The correctness of this viewpoint is supported by simi-

TABLE VI. RELATION OF PRETREATMENT MENSTRUATION TO RESPONSE TO LOW-DOSAGE IRRADIATION IN 90 AMENORRHEAL WOMEN

TYPE OF PRETREATMENT MENSTRUATION	NO. OF PATIENTS	CURED	
		NUMBER	PERCENTAGE
Spontaneous	53	41	77.3
After estrogen	32	22	68.7
None	5	1	20.0

larity in response of the patients to x-ray therapy irrespective of the type of pretreatment bleeding, spontaneous or estrogen evoked. Failure of the uterus to bleed following such preliminary steroidal therapy should, on the other hand, be regarded as a contraindication to low-dosage irradiation (Table VI).

Subsequent Pregnancies.—The follow-up period of this study, as mentioned previously, was arbitrarily taken as one year from the time of completion of low-dosage irradiation. During the year of follow-up, 27 of the 90 patients conceived; 24 of the 27 pregnancies began within six months of treatment (Table VII). Such a high rate of conception is not common in women with an untreated menstrual disorder but is more in keeping with the rate expected of the random female population.[39, 40] The frequency of immediate conception in the group herein reported tends to support the enthusiastic statement of Collins,[1] whose experience was similar, to the effect that "women are six times more liable to pregnancy from this treatment alone."

TABLE VII. PREGNANCY OCCURRING WITHIN ONE YEAR OF LOW-DOSAGE IRRADIATION IN 90 AMENORRHEAL WOMEN

NO. OF REGULAR PERIODS BETWEEN X-RAY THERAPY AND ONSET OF PREGNANCY	NUMBER OF PREGNANCIES	OUTCOME OF PREGNANCIES			
		NORMAL BABY	ABNORMAL BABY	ABORTION	ECTOPIC
None	3	2	1*		
1-3	8	5		2	1
4-6	13	13			
7-12	3	3			
Total	27	23	1	2	1

*Microcephalic, conceived during course of x-ray treatments (see case report).

The fact that 3 of the 27 pregnancies occurred following x-ray treatment without an intervening menstrual flow is of great practical significance. The presence of early pregnancy in an amenorrheal woman is easily overlooked. Such a patient may believe her amenorrhea either uncured or made worse following irradiation. In each of the 3 instances mentioned, the diagnosis of pregnancy was not sought by the patient and was not established until the second trimester. One reported seeking relief from continuous nausea, the second because of an enlarging abdomen, and the third came to request further treatment of her amenorrhea. These experiences stress the value of examining the patient two months following completion of x-ray treatment, more particularly if she has not menstruated by that time.

Since gestation occurring in women who conceive despite untreated menstrual disorders tends to a high rate of disaster, the outcome of the 27 pregnancies which followed low-dosage irradiation is of interest. It may be seen from Table VII that 23 of the 27 pregnancies eventuated in normal babies. The advent, however, of a single abnormally formed baby in such a series cannot be overlooked. Moreover, it is of especial interest when the history of that pregnancy is detailed.

CASE HISTORY.—Mrs. A. T. was first seen in 1941 at the age of 22 because of oligomenorrhea in association with involuntary barrenness. Investigation failed to reveal an explanation or infertility in either partner, other than the apparent menstrual disorder. The

patient's menarche had occurred at the age of 11, her periods continuing at intervals varying from five to eight weeks until the age of 20, when the cycles lengthened to an average of ten weeks. The patient sought aid after oligomenorrhea had been present for two years. Having completed a menstrual flow on April 24, 1941, she was referred to the radiologist for low-dosage irradiation and was instructed to employ contraception until the course of therapy had been completed. The customary three treatments were administered on April 25, May 2, and May 11, 1941, following which no menstruation occurred. Examination on June 17, 7941, revealed the patient to be approximately five weeks gravid, at which time she confessed to having had unprotected intercourse on April 27 and April 29. The pregnancy continued uneventfully to term, concluding on Feb. 9, 1942, with the spontaneous birth of a microcephalic male child, weighing six and one-half pounds, who lived but two months. In retrospect, it is apparent that the patient received the second and third roentgen treatments after she had conceived, leaving little doubt that the microcephaly may be ascribed to the irradiation. Fortunately, this patient has been delivered subsequently of two normal children, supporting Murphy's[30, 33] concept of the difference between the effects of pre- and postconceptional irradiation.

Summary and Conclusions

The favorable response of selected amenorrheal women to low-dosage irradiation of the pituitary gland and ovaries is undisputed in recent literature. Interest in such therapy, however, does not rest primarily on its therapeutic efficiency but centers on questions of its mode of action, safety, and of the possibility of its delayed effects on posterity. The physiologic basis for the apparent effectiveness of irradiation in secondary amenorrhea, as well as in the associated infertility, is presently inexplicable. None of the manifold theoretical explanations is susceptible of proof. Many investigators, including the author, have subjected animals to similar irradiation and have failed to find morphologic changes, in the absence of which it is impossible to establish a relation of cause and effect.

Proper selection of patients and fixed low dosage assure the method's immediate safety. Late genetic sequelae have been imputed to low-dosage ovarian irradiation because of certain observations in animals. Recent studies, however, show that experimental data may not be relied upon to predict the occurrence of induced genetic changes in man. This thesis is supported by the fact that the quantity of x-rays administered to animals has been not only too large in comparison to the quantity administered in low-dosage therapy but also has been of the whole-body type. The latter technique makes it particularly difficult to collate experimental observations and clinical results.

The present report comprises an analysis of results obtained in 124 patients subjected to x-ray therapy because of secondary amenorrhea during the fifteen-year period, 1936 through 1950, from the author's private practice. The presence of only one ovary, adolescence, and the possibility of pregnancy were regarded as contraindications to treatment. The necessity of avoiding conception until the three treatments have been completed is stressed. The compelling nature of this advice is illustrated by the single unfortunate administration of therapy during the early days of pregnancy which terminated in birth of a microcephalic child.

The technique employed included one treatment of from 50 to 80 r (air) per week for three consecutive weeks, the pituitary and ovaries being irradiated at each sitting.

In sifting the observations, it was found necessary to omit 34 patients: 4 for failing to complete the required course of treatment, 10 because of incomplete follow-up, and 20 for having had closely antecedent therapy. Sixty-four of the remaining 90 patients (71.1 per cent) either attained cyclic menses for at least one year or achieved pregnancy following the treatment. No relation was apparent between the age of the patients (from 20 to 35 years) and their response. However, the degree of amenorrhea was noted to be an important factor, the cure rate being inversely proportionate to the length of the menstrual interval. The experiences recorded, moreover, emphasize the value of not initiating x-ray treatment until the patient has menstruated, either spontaneously or through artificial means.

Twenty-seven of the 90 patients became pregnant during the course of one year following x-ray treatment, 23 of whom gave birth to normal children at term. Three of the 27 pregnancies began without an intervening period, exemplifying the importance of examining patients who do not menstruate within several months of treatment.

It is averred that these data support the contention that low-dosage irradiation may be safely employed in properly selected patients and reaffirm its effectiveness in secondary amenorrhea, even though on an empiric basis.

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Discussion

DR. ERNEST W. PAGE, San Francisco, Calif. (by invitation).—Dr. Israel has presented this subject of low-dosage irradiation very ably and in a most objective manner. The very title, which wisely employs the word "empiric," exposes our ignorance of what we are doing. Yet his cure rate of 71 per cent and his pregnancy rate of 30 per cent in women who presumably do not ovulate spontaneously is not an isolated clinical testimony. In a score of papers published in the past decade, the functional cure rates are between 50 and 80 per cent, and the number of pregnancies occurring within one year of treatment range from 25 to 50 per cent. It is noteworthy that no one to date has reported a sizable series with poor clinical results.

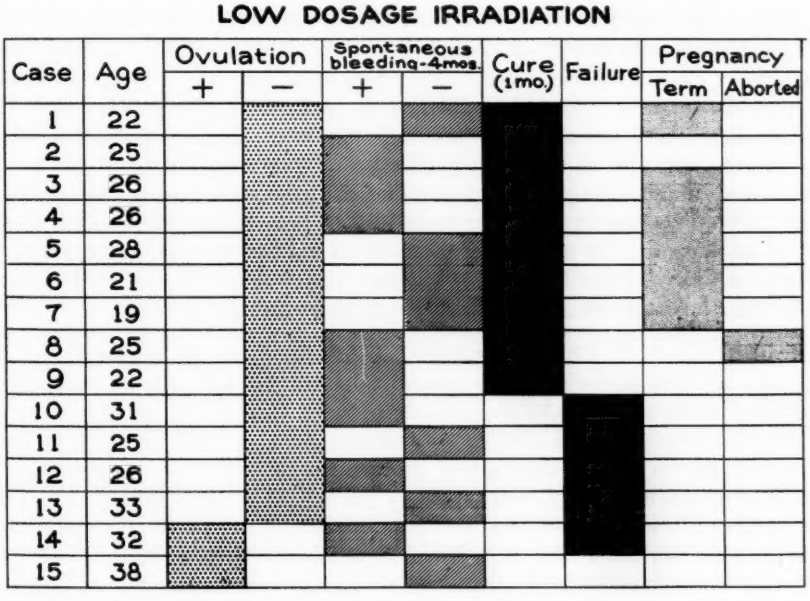

Fig. 1.

The success of this method is certainly not due to chance. For fifteen years I have struggled with the problem of ovulatory failure, using every mode of endocrine therapy. The cure rate has been less than 25 per cent, and the pregnancy rate far below that. Collins concluded from his questionnaire survey that only 30 per cent of American gynecologists use this method. Most of the others had been frightened away by fruit flies, mice, or men. Some five years ago, partly out of desperation, I joined the minority group, and have since used the method in 15 cases. They can be summarized on a single slide.

The first two columns represent the functional status of each patient prior to therapy, while the last two show the results. These women complained of sterility, and had been

observed for at least 6 months to establish the presence or absence of ovulation. All but two had complete ovulatory failure, as indicated by a continuous flat basal body temperature for 6 months. Seven were amenorrheic, as indicated in the second column, while others had periodic, though irregular bleeding. Cyclic steroid and gonadotrophic therapy was used initially in all, and had failed. The last two cases were not wisely chosen because of their age and physiologic status.

As indicated in the next column, 9 of the 15 were functionally cured, meaning that each one ovulated within three weeks after completion of the x-ray therapy, and continued to have normal cycles therafter. Seven of the nine became pregnant within eight months. One aborted, but had a child the following year. The children were healthy, and their mothers are not at all impressed by the irrationality or unscientific nature of the treatment.

This experience is admittedly very meager, but suggests to me that perhaps we should limit the treatment to women who are (1) between the ages of 20 and 30, (2) whose chief complaint is sterility, (3) who have proved ovulatory failure, and (4) in whom accepted methods of endocrine treatment have failed. I wonder if Dr. Israel has data relative to the question of ovulation in his oligomenorrheic patients, and whether he believes all other methods should be exhausted before resorting to the x-ray.

The pituitary gland, so advantageously concealed from most surgeons, cannot readily be damaged by the radiologists. We recently conducted endocrine assays on three cancer patients before and after receiving up to 12,000 r to the pituitary without finding any evidence of hypofunction. Just what 100 r could accomplish is a complete mystery.

In the case of the ovaries, perhaps the radiation does what Dr. Stein's knife accomplishes. Six months ago, we treated a girl who had hirsutism, amenorrhea, and bilaterally enlarged ovaries with low-dosage irradiation in lieu of surgery, and she is now four months pregnant.

The possible genetic effect of irradiation is in part a philosophic question, namely, how many roentgens can stand on the head of an ovum? Evans, of Boston, recently calculated that if 5 per cent of the total population of the world received 280 r total body irradiation before childbearing (more than twice the amount we use), the resultant anomalies after 2,000 years would be 8 per cent higher than the expected spontaneous rate. This worries me a little, but not nearly so much as our atomic energy program. Perhaps our great-grandchildren, should they survive the atomic age, will smile a bit amusedly at our great anxiety over the 100 r given their great-grandmothers' gonads.

DR. HOUSTON S. EVERETT, Baltimore, Md.—If I take an aspirin tablet, I get the hives, but that is no reason why others cannot take aspirin, and it is no reason for me not to take aspirin, because if I take pyribenzamine with it, I don't get the hives. I think there are no therapeutic agents that do not have a hármful reaction in some individuals, and that is my reason for talking about the aspirin tablet. I know nothing about the technique of irradiation therapy, but for many years I have been following the results of irradiation therapy in patients so treated for carcinoma of the cervix. A good many years ago and before we had the excellent services of Dr. Jones, I was interested in the subject that Dr. Israel has talked about today. We treated a few cases, and we had some good results. We discontinued the method because we could not keep the members of the Radiologic Department interested enough to work with us, but while we were doing that we had at least one bad result. We were not only treating patients for amenorrhea and sterility but also for functional menorrhagia. We used low dosage and we got good results, except in one girl who had the same dosage as the others, but who developed a permanent amenorrhea with terrific hot flashes. So we had a permanent menopause persisting in a young woman.

My experience with higher dosage irradiation in the treatment of carcinoma of the cervix has convinced me that there are some individuals who are supersensitive to the effect of x-rays. I have talked twice previously before this Society on the effects of such treatment on the urinary tract. Most of the patients with serious complications had not

had greater dosage of irradiation than others who had no ill effects, so I think this therapeutic agent has to be considered as having an undesirable effect on patients who are supersensitive to it. I think it would be a great advantage if some method could be developed by which we could detect supersensitivity analagous to the test we do before we give Diodrast. An occasional case has been reported of anaphylactic shock and death from this substance, so by subcutaneous injection of a small amount of Diodrast we can detect if the patient is sensitive to it. Some such simple test to detect hypersensitivity to irradiation would be of tremendous help in the use of irradiation therapy.

In a patient with carcinoma of the cervix Dr. Schmitz said, at the recent Obstetric Congress in Cincinnati, that one of his criteria for operation was resistance of the tumor to irradiation therapy. If the patient should be hypersensitive to irradiation the normal tissues will probably not tolerate sufficient therapy to eradicate the tumor, so that in patients of this type operative treatment should also be seriously considered. Another approach, and one on which a member of our department is working now in conjunction with the Radiology Department, is some method by which we can prevent these untoward reactions to irradiation, just as in my case pyribenzamine will prevent hives from aspirin.

DR. LAWRENCE M. RANDALL, Rochester, Minn.—I can sympathize considerably with Dr. Israel's remarks because I have defended this form of treatment for a good many years and I bear some scars as the result of some of the battles. I think, however, if we could have more presentations such as he gave this morning, we would come to a better understanding of the matter and, as has been said, I think we have been chased by the fruit fly more than we should. There will continue to be a debate about the possible side effects, but it seems that we have accumulated sufficient clinical experience to indicate that the method can be used safely and effectively. Dr. Drips commenced our interest in this form of therapy in 1926 and has accumulated a great many data. I mention this work because I believe we have given this method of treatment a more severe trial than has Dr. Israel. We have two groups of patients, one in whom the amenorrhea was due to a pituitary failure with a duration of one to ten years. These were treated only with low-voltage irradiation to the pituitary and ovary with 75 per cent improvement in function for a few months to over one year. The other group were young women whose amenorrhea was due to failure of the ovaries and not primarily failure of the pituitary. The success in this group was only 39 per cent. It seems to me that if one can take a group of young women who have failed to menstruate for a year and treat them only by this method and can produce menstruation and pregnancy, then we have a therapeutic agent that should not be neglected.

The question of amenorrhea as a *symptom* I think is something we should consider seriously and keep one thing in mind. We quite frequently pick up a young woman with amenorrhea in whom the amenorrhea is the first symptom of a pituitary tumor. So all of these patients who are irradiated have x-ray films of the pituitary gland first.

It seems to me that we should make an attempt to differentiate the primary source of amenorrhea. We have not felt in many of the patients with oligomenorrhea that this form of therapy was necessary. In patients with established amenorrhea, on the other hand, and in whom other forms of therapy have not succeeded, we have used irradiation. If the condition is due to primary pituitary failure, we treat the pituitary and the ovaries. On the other hand, if it is due to ovarian failure, most of them have excessive pituitary hormones so why treat the pituitary?

As to the question of prognosis, we have done much better with the group whose amenorrhea was due to pituitary failure than we have in the group whose amenorrhea was due to primary failure of the ovaries. That is logical because if in the healthy girl the ovary fails to function you are probably dealing with an ovary of poor quality.

I want to make it quite plain that I believe the basic treatment for amenorrheal dysfunction in the young woman is improvement in nutrition, proper adjustment of weight, thyroid extract where indicated, the use of steroids cyclically to prime the endometrium

and help restore the pituitary-gonad axis. This will result in a fair amount of salvage. If, on the other hand, it does not succeed, we are justified in giving these patients low-voltage irradiation.

MR. T. N. A. JEFFCOATE, Liverpool, England (by invitation).—I feel I should like to take the opportunity to discuss a paper on this program and this particular subject interests me, although not because I have any expeirence in radiotherapy. In fact, this method of treatment of amenorrhea is hardly ever used in Great Britain for the usual reasons which have been mentioned this morning. The first is that it is empiric and the second is the theoretical risk—and I think the literature makes it quite clear that the risk is theoretical. But there is a third objection, I think, to the use of radiotherapy and it is one which is tinged skepticism: Is this form of treatment necessary or effective? It is very difficult to assay the results of any method of therapy for amenorrhea. In fact, we might ask, when is amenorrhea amenorrhea? If a woman ceases to menstruate for three or four months is she amenorrheic? Have we any guarantee that she will not start menstruating again spontaneously? Amenorrhea has been pointed out to be a symptom with many causes and it is, therefore, very difficult to take a big group of cases and label them all amenorrhea and consider the results. It is worth pointing out that most workers showing excellent results for radiotherapy make a point of their selection of cases. They exclude primary amenorrhea. Many exclude secondary amenorrhea in the older patients and, if I understood the essayist correctly, he also excludes those cases in which there is reason to believe the ovaries are infantile and includes only those cases in which the uterus has been shown to respond readily to hormones. So we are dealing only with those patients who respond best to any sort of treatment anl those which often cure themselves. Spontaneous cure of short-term amenorrhea is a very common thing and so is spontaneous cure of infertility in these cases. I have no figures to offer in support of this argument but they are available in the literature, and they go to show that for women below the age of thirty with secondary amenorrhea lasting even one year, a cure rate of 60 per cent is to be expected irrespective of the method of treatment—psychotherapy, physical therapy, or hormones.

Be that as it may, if radiotherapy does cure amenorrhea, we still have the fascinating problem of why does it work? I want to throw out a suggestion which is perhaps a new approach. The idea occurred to me when hearing Dr. Selye talk on ACTH and the stress factor. He emphasized that in early experimental work in that field one of the methods of applying stress was to expose the subject to x-rays. The effect of any sort of x-ray exposure is to produce disturbance in the endocrine system, particularly in the pituitary, the adrenals, and ovaries. Does radiotherapy, therefore, influence amenorrhea because it is applied to the pituitary and the ovaries or merely because it is applied to any part of the body? Carrying the argument to extremes, it might be said that perhaps exposure of the big toe to x-ray might work just as well as exposure of the pituitary. I wonder if the workers in this field have controlled their work in any way by irradiating different parts of the body other than these glands.

DR. CARL P. HUBER, Indianapolis, Ind.—I would like to record one isolated observation and incidentally thank Mr. Jeffcoate for the splendid introduction he made to my remarks. We have a series quite comparable to that of Dr. Israel; sixty patients treated with low-dosage irradiation, all of them patients in whom various types of therapy and careful investigation had preceded the irradiation. We wondered what actual effect the x-ray might be having on these patients. We chose a patient whose primary complaint was infertility; she had been married five years, failed to conceive, had irregular periods with occasional episodes of profuse bleeding and with longer periods without menstruation. This patient was scheduled for low-dosage irradiation and she was told what the results had been in other patients in the past. She was accurately calibrated and irradiation was given except that a filter was placed so that the patient received no x-ray therapy. She had one menstrual period, conceived the following month, and delivered a normal baby.

DR. ISRAEL (Closing).—The selection of a single facet of this type of therapy was deliberate. I did not wish to becloud the issue with patients whose complaint was infertility, irregular bleeding, or anovulatory infertility. The attempt was made to treat, for purposes of this discussion, a single entity: secondary amenorrhea.

In regard to Dr. Page's question whether or not data are available concerning the occurrence of ovulation in these patients, they are not available. My experience in employing this agent for relief of anovulatory menstruation as a factor in sterility is not good. I prefer to use other agents. Dr. Page also raises the embarrassing question which we might discuss at another time: What other agents? At the present time the best we have is the alternative, high-dosage steroid therapy.

In regard to Dr. Everett's point that possibly some patients are more sensitive than others, that is a comment which cannot be answered. I do yield that there may be an occasional patient who will go into permanent amenorrhea from this therapy. I have specific figures for a larger group of patients who were treated with this therapy who did just that: 7 out of 480 became permanently amenorrheic. That experience is what made us come to the conclusion that when the patients are selected carefully according to age and severity of the disorder, it is less likely to happen.

I am quite familiar with Dr. Randall's point and Dr. Drips' work. It was quite a struggle on my part to decide whether or not to include in this discussion patients who were treated solely to the pituitary or solely to the ovary. It seemed to be more honest to report the experiences as we had them. These patients were subjected to therapy without endocrine assay and without selection as to etiology of the amenorrhea; Dr. Randall knows I agree with him that the latter is important. But the patients were treated at random according to the factors outlined. There is no question that if you select patients on the basis of etiology of the amenorrhea, the results will probably be a little bit better in the pituitary group than in the ovarian group. It is interesting in this connection, and I am privileged here to quote some unpublished material of Rakoff at Jefferson, that patients with primary ovarian amenorrhea show an increase in estrogen excretion and decrease in gonadotropin excretion almost immediately following irradiation of the ovaries. This supports Dr. Randall's thesis.

I am familiar with Mr. Jeffcoate's philosophical argument about "big toe" irradiation. About fifteen years ago we treated 50 patients with low-dosage irradiation following the technique of Dr. Huber: putting a filter between the machine and the patient. The results in that group were not at all comparable, and I am sorry I do not have the figures with me. But if Dr. Huber will project that treatment to more than one patient, he will find the results are not comparable.

CURRENT CONCEPTS OF PROLONGED OR IRREGULAR ENDOMETRIAL SHEDDING*

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WHILE the evidence indicating that irregular shedding is a major functional disturbance of the endometrium has been well documented,[1, 2] this variety of functional bleeding has not yet achieved the general acceptance which it merits. To demonstrate how irregular shedding produces abnormal uterine bleeding and to substantiate its position as a gynecological entity, we wish to contribute our recent experiences with this diagnostic problem as it has been encountered on the gynecological service at Stanford University Hospitals. The pertinent literature has been reviewed elsewhere.[2] The only major contributions of more recent date have been the attempt by Masters and Magallon[3] to produce irregular shedding experimentally in postmenopausal women, and the restatement of clinical and histopathologic features by McKelvey.[4]

Although the term *irregular shedding* is inadequate to convey the impression of a *prolonged* period of endometrial desquamation recurring in cyclic fashion, there seems to be no wholly suitable designation which is not objectionable on the grounds of being altogether too cumbersome for clinical usage. Fluhmann,[5] for example, has referred to "prolonged defective desquamation," a phrase meaningful to the histologist but probably not to most clinicians. Assuming that one comprehends both the histologic and clinical features embraced by the phrase, irregular shedding of the endometrium, this would seem to be as satisfactory a name as any. Obviously it has the advantage of long usage. It must be emphasized, however, that the word *irregular* refers to the appearance of the endometrial surface and not to the tempo of the bleeding. Indeed, one of the most characteristic things about irregular shedding is the regularly recurring menorrhagia; that is, an accentuation, with respect to duration and quantity, of the previously normal and regular cyclic menstrual bleedings.

Pathological Material

In the past four years the diagnosis of irregular shedding was made on 75 endometrial specimens examined in the departmental pathology laboratory. These specimens came from 71 different women, 4 of whom demonstrated irregular shedding on each of two occasions. Twenty-two specimens have been eliminated from further consideration either because they were merely endometrial biopsy specimens (without subsequent complete curettement) or because the accompaning histories were atypical. They are mentioned only

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to give a more adequate concept of the frequency with which this diagnosis is ventured. Careful review of these discarded specimens suggests that most of them actually were from uteri with irregular shedding, but we believe that material from the entire endometrial area should be inspected before this diagnosis is accepted as correct and final. Similarly, one should insist that a plausible history of menorrhagia be furnished and that the specimen be accurately dated with reference to the menstrual cycle (see below, under Timing of Curettage). The histopathologic details necessary for the diagnosis of irregular shedding have been described fully in previous publications[1, 2, 4] and they will not be repeated here.

Of the 53 acceptable specimens, 25 were from private patients and 28 from patients on the clinic service. Since 4 patients were subjected to curettage or biopsy on two different occasions, only 49 different women are involved in the compilations which follow. Twelve of the 23 private patients were from the practice of the writer and the remaining 11 were cared for by seven other gynecologists. The total absence of irregular shedding from the practices of some of the members of our staff may be attributed in all likelihood to improper timing of curettements in patients with suggestive histories.

Clinical Information

1. Age.—Only 2 patients were less than 20 years of age and one was over 50. The remainder were rather evenly distributed among the three decades of life between 20 and 50 as follows: 20-29 years, 17 cases; 30-39 years, 13 cases; and 40-49 years, 16 cases. Unlike endometrial hyperplasia, irregular shedding of the endometrium shows no affinity for adolescent girls and menopausal women.

2. Parity.—Twelve of the 49 patients had never been pregnant, and 13 of them had produced only a single child. In the remaining half of the group, parity ranged from two to seven. While a few of the parous women developed the menorrhagia of irregular shedding shortly after delivery, the time relationship to pregnancy was not a striking feature in at least 90 per cent of our patients.

3. Duration and Amount of Bleeding.—No definite number of days may be set down as characteristic, because in many patients there is a variation of several days from period to period. One week of bleeding has been accepted as the minimum time consistent with a diagnosis of irregular shedding, but the common experience is a duration of flow ranging from nine to twelve days. Three patients bled longer than twelve days nearly every month. Despite the unusual amount of time devoted to bleeding, the total length of the cycle customarily does not change. While seven days may be considered the upper limit for normal menstrual bleeding, it is by no means usual for most women to bleed for so long a time. Thus prolongation of flow to seven days often represents a distinct change in menstrual habit. Ordinarily there is in addition an appreciable increase in the quantity of bleeding, being most noticeable on the second and third days of the cycle but frequently persisting into the fourth or fifth day. Many patients complained of the necessity of wearing two perineal pads simultaneously, whereas previously one had been more than adequate.

4. Timing of Curettage.—In all but 5 cases the endometrial specimens were obtained on the fifth day of the cycle or later, but in only three beyond the tenth day of bleeding. Five specimens obtained on the fourth day of bleeding have been included inasmuch as the histologic features were distinctive and the accompanying histories were appropriate. We prefer to obtain curettings on the fifth or sixth day of bleeding, since the volume of

residual endometrium at that time is still appreciable if irregular shedding exists, yet one is well beyond the time when regeneration of a new proliferative surface will be found in most normal women.[6] In this connection it is interesting that Bartelmez[7] very recently has found the endometrial surface in the Rhesus monkey, like that in the human being, to be restored by the fourth day of menstrual bleeding.

5. Associated Uterine Lesions.—Eight of the 49 women had myomas and one had, in addition, an endometrial polyp. While these lesions may contribute to the production of menorrhagia, it is unlikely that their presence was in any way responsible for delay in shedding of endometrium from the entire uterine cavity. Six of the patients with myomas were over 40 years of age, and it seems reasonable that at this time of life the tumors were merely coincidental findings. One patient later was shown to have ovarian endometriosis, but at the time of laparotomy no gross involvement of the uterus was seen and it was not removed.

Incidence

No valid expression of the incidence of irregular shedding among gynecologic patients is currently available. Because this is a lesion which may be found only during a particular portion of the menstrual cycle, it is not going to be turned up unless it is specifically sought. By no means all of the curettages (or hysterectomies) in our clinic patients were carefully planned as part of a program to distinguish irregular shedding from other common causes of menorrhagia, although such planning by and large was more prevalent in the clinic than on the private service. Had such foresight been practiced more universally in dealing with patients admitted to hospital for curettage, it is likely that many more cases would have been brought to light. Suffice it to say that in our clinic clientele irregular shedding is becoming a rather commonplace finding, as more precise knowledge of its specifications permeates the resident staff.

In my own private material, 12 patients with irregular shedding have been found among the last 80 women who were curetted in an effort to diagnose abnormalities of bleeding (excluding malignant disease and obvious incomplete abortions). In other words, irregular shedding has accounted for about 15 per cent of the bleeding disturbances in these patients, disorders which would not have been recognized in most instances if the curettage had not been carefully timed.

Case Reports

It is not feasible to include details concerning the entire 49 patients whose endometria have been studied. To demonstrate various aspects of the situation, the pertinent facts relating to four patients are recorded here.

Case 1.—M. C. (Hosp. No. E-70545), aged 37 years, para iii, gravida viii, was first seen in September, 1948, complaining of menorrhagia for nine years. Her menstrual cycle was 30 to 31 days, but the bleeding phase lasted regularly 7 to 10 days and occasionally as long as 14 days, with three or four days of preliminary spotting. The first five days of flow were profuse. A trachelorrhaphy, uterine suspension, and bilateral tubal ligation had been done several years previously and she had recently been urged to submit to hysterectomy because of the scarred cervix and profuse bleeding. Examination disclosed no abnormalities other than a shortened and irregular cervix.

Curettage done on the fifth day of the next menstrual period revealed endometrial tissue consistent with a diagnosis of irregular shedding (Figs. 1 and 2). Subsequent bleedings came at intervals of 26 to 32 days, with a duration of five days, and scanty to moderate flow. However, in March, 1951, premenstrual spotting persisted for five days and the flow lasted nine additional days. Since this pattern was repeated in April, curettage was done again in May, 1951, on the fifth day of bleeding and the endometrium was similar to that found in 1948. During the past year menses have appeared at monthly intervals and the duration has been five to seven days on each occasion.

Fig. 1.

Fig. 2.

Fig. 1 (Case 1).—Portion of endometrial fragment removed by curettage on fifth day of menstrual bleeding, showing secretory glands in a contracted stroma and numerous blood vessels cut in cross-section.

Fig. 2 (Case 1).—Higher magnification of collapsing secretory glands shown in upper left-hand portion of Fig. 1.

CASE 2.—R. W. (Hosp. No. E-87424), aged 42 years, para ii, was first seen in October, 1950, because of menorrhagia, dysmenorrhea, and premenstrual tension. For two years her periods had been prolonged to eight or nine days, whereas formerly she had bled four or five days at monthly intervals. Menstrual cramps, absent since the birth of her first child eighteen years previously, had reappeared and there were many disturbing symptoms during the week preceding each period. Examination revealed a retroverted uterus which could be brought forward easily and a small (2 to 3 cm.) subserous myoma in the fundal region. Hysterectomy had been advised because of the profuse bleeding.

Curettage was done on Nov. 17, 1950, which was the sixth day of the next menstrual period, and tissue compatible with a diagnosis of irregular shedding was recovered. The

subsequent bleeding began on Dec. 11, 1950, lasted only five days, and was not painful. In the past year and a half menses have been entirely normal and premenstrual symptoms have been notably absent. Recent examination showed no change in the size of the myoma.

Fig. 3.

Fig. 4.

Fig. 3 (Case 3).—Portion of large endometrial strip removed by curette on seventh day of menstrual bleeding. Note secretory pattern of glands, relatively dense stroma, and spiral arteriole at top to left of center.

Fig. 4 (Case 3).—Another area from endometrium shown in Fig. 2. Note so-called "star-shaped" glands often seen in the retained secretory endometrium of irregular shedding.

CASE 3.—M. R. (Hosp. No. 287430), aged 20 years, para ii, delivered her second child in May, 1948. In the fall of that year her menses became profuse and prolonged, although she still had a regular cycle of 32 to 35 days. In January and February, 1949, she bled 11 and 12 days, respectively, and in March an endometrial biopsy taken on the sixth day of bleeding suggested a diagnosis of irregular shedding. In April a complete curettage on the seventh day of bleeding produced large fragments of retained secretory endometrium (Figs. 3 and 4). No other plevic abnormalities were found. In subsequent months the menses were normal and she became pregnant again nearly two years after the curettement. Her third child was delivered at Stanford Hospital in October, 1951.

CASE 4.—A. J. (Hosp. No. E-84222), aged 40 years, para ii, had been delivered twice by cesarean section and had been surgically sterilized by tubal ligation after the second delivery in 1948. Two years later she consulted her private physician in January because of menorrhagia which had been exhibited with each menstrual flow for eight months. She was treated empirically with hormones (estrogens and progesterone) during four successive months but without any specific therapeutic plan. Profuse and prolonged menses continued as before, with cycles of 28 to 30 days in length and 9 to 14 days devoted to

bleeding. Because of this lack of response to conservative treatment, hysterectomy was done on June 20, six weeks after the last horomone therapy and on the fifth day of the menstrual flow, thus providing us quite inadvertently with one of our choicest specimens of irregular shedding. The uterus was grossly normal, but microscopic sections of the endometrium showed an extraordinary degree of retention of secretory endometrium and complete absence of endometrial surface (Figs. 5 and 6).

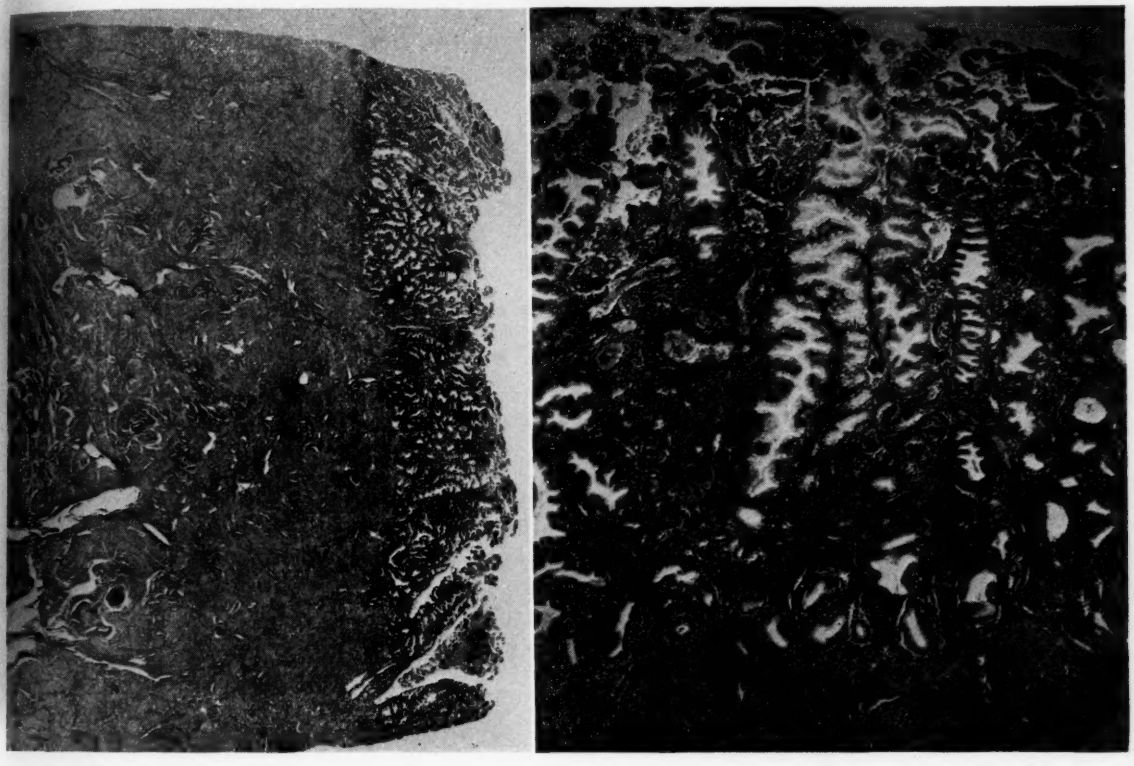

Fig. 5. Fig. 6.

Fig. 5 (Case 4).—Low-power view through segment of endometrium and subjacent myometrium, showing unusual retention of secretory endometrium on fifth day of menstrual period. Hysterectomy specimen.

Fig. 6 (Case 4).—Higher-power view of portion of fifth day endometrium shown in Fig. 4. Note large vascular spaces and extensive secretory effect extending almost to the muscularis. Endometrial surface has been shed.

Subsequent Course

Eight of our 49 patients subsequently had their uteri removed. Five of these hysterectomies were done because of myomas, and were performed anywhere from a few days up to as long as four years after the diagnostic curettage. One patient had a hysterectomy in conjunction with removal of an ovarian cystoma, and one had a cesarean hysterectomy at the time of delivery of her fourth child. She had conceived three months after the curettage for irregular shedding, having been infertile for a period of six years. The remaining patient was subjected to hysterectomy eight days after curettage, for reasons which are not at all clear beyond the fact that a sanguineous discharge persisted. The endometrium at that time showed early proliferation with an intact surface and it seems likely that removal of the uterus was not essential for hemostasis.

Five patients were lost track of immediately after curettage and cannot momentarily be located. Four of the specimens of irregular shedding were first seen in removed uteri (as, for example, Case 4) and these obviously cannot be considered further. Thus, 32 patients remain for review and it appears that all of these were benefited by curettage. While the period of follow-up varies from as little as three months to almost four years, it may be said that none had an immediate recurrence of menorrhagia.

Only 2 of the entire group were curetted a second time because of recurring menorrhagia, the first one after a lapse of two and one-half years (Case 1), and the other after an interval of fourteen months. This latter patient was then given a sterilizing course of x-ray therapy (she was 46 years of age) and has had no further uterine bleeding. Two other patients were subjected to endometrial biopsy a month before the curettage (see above, under Pathological Material), which was then done as a therapeutic procedure when menorrhagia recurred.

Comment

When this group of 49 patients is compared with the 34 cases reported by McKelvey and Samuels[1] in Minnesota, or the 22 in Holmstrom's[2] series from Utah, there are striking similarities in age, parity, duration of bleeding, and associated pelvic lesions. McKelvey's material, however, included 9 patients whose menstrual cycles were "too irregular to classify" and another 8 patients with cycles of less than 25 days in length. We have been quite rigid in the matter of excluding patients with irregular cycles because it has seemed desirable as a teaching exercise to limit our search for irregular shedding to those women who demonstrate the classical picture of regularly recurring menorrhagia, but there is no doubt that the histologic features of prolonged shedding may be found on occasion in other patients. Indeed, some of the 22 specimens which were excluded from this study (see above) were eliminated solely on the basis of marked irregularity of the bleeding pattern. There would seem to be, then, considerable numbers of patients living in widely separated parts of the country who present identical complaints and identical findings. It is likely that their distribution is more universal than one would suspect from looking at textbook literature and that they have been masquerading under other diagnoses.

The etiology of irregular shedding remains obscure, although it seems clearly to be related to persistence of corpus luteum activity well into the bleeding phase of the cycle. Judging from the excellent secretory effect seen in most of the endometria associated with irregular shedding, the suggestion that the corpus luteum produces inadequate amounts of progesterone and permits "breakthrough" bleeding seems unlikely.[3] The alternative suggestion that a normal or even hyperactive corpus luteum of menstruation involutes slowly appears more logical, although any explanation of why this should occur is just as inadequate as the usual explanations for persistence of follicular activity in women with endometrial hyperplasia. Assuming, however, that incomplete progesterone withdrawal provides a basis for irregular shed-

ding, one may go further—as Holmstrom and Jones[8] have done—and postulate that production of pituitary FSH is inhibited. This may result in delayed follicular development, inadequate amounts of estrogens, and ultimately delay in regeneration of the endometrium.

In view of our inadequate knowledge of the precise mechanisms responsible for normal endometrial bleeding, such speculations may be premature. When the missing links, chemical or otherwise, in the process of menstruation are found, it is likely that the basis for dysfunctional bleeding will be clear. Yet we need not await these fuller explanations before acknowledging irregular shedding as a clinical entity of considerable usefulness in relation to menorrhagia, and one which is readily controlled by a simple operative procedure.

McKelvey has stressed the fact that the endometrial arterioles found in specimens of irregular shedding often appear thicker, and therefore older, than would be anticipated if they had been developed during only a single menstrual cycle. Phelps[9] has indicated that the vascular architecture existing at the beginning of any single cycle has a decided influence upon the duration of bleeding in that cycle. It is possible, then, that irregular shedding perpetuates itself and even increases in degree owing to this phenomenon of abnormal vascular retention in the functionalis month after month. And in all likelihood the good results achieved by curettage alone are due in large part to the removal of a persistent vascular network which resists the usual processes associated with desquamation of endometrial tissues.

Regarding treatment, it has been suggested[3] that 25 mg. of progesterone for two or three days would effect a chemical curettage after producing luteal changes in the remaining endometrium. While such a sequence of events may occur in the experimental subject without endogenous progesterone production, one wonders whether it would regularly be effective in the patient who is already excreting pregnandiol beyond that time in the cycle when progesterone metabolism ordinarily has ceased. The administration of estrogens, beginning a few days prior to the end of the cycle and continuing through the bleeding phase, also has been advised.[8] Perhaps this would be an ideal situation for the use of estrogenic substances by the intravenous route.[10] Neither of these hormonal therapies has been given an adequate trial as yet, very largely because curettage alone has produced such satisfactory results in the majority of instances. But certainly we must explore newer devices for the control of irregular shedding in patients for whom curettage is inadequate and who have no valid organic indications for hysterectomy. Since many of these women are young, x-ray sterilization is only occasionally a satisfactory solution to the problem of continued excessive bleeding.

Summary

In four years 75 specimens of endometria showing the characteristic picture of irregular (prolonged) shedding were seen in the gynecological pathology laboratory at Stanford University Hospitals. Eliminating biopsy speci-

mens, duplications of patients, and those with atypical histories, 49 cases remained for study. In this group, the largest series yet reported, clinical characteristics were essentially those previously described. Irregular shedding is typically a regularly recurring menorrhagia in which the bleeding phase of the cycle requires seven to fourteen days for completion, without subsequent prolongation of the cycle. The diagnosis is made by recovering retained secretory endometrium five or more days after the onset of menstrual bleeding. This disorder probably accounts for at least 15 per cent of the instances of abnormal uterine bleeding not associated with disordered pregnancy or malignancy.

Details of four instructive cases are presented and illustrated. Etiological factors are discussed and therapeutic suggestions, other than curettage and hysterectomy, are noted for future trial.

The widespread occurrence of irregular shedding of the endometrium, and its adaptability as an explanation for selected examples of menorrhagia warrant its more general acceptance as a major variety of dysfunctional uterine bleeding.

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Discussion

DR. LAWRENCE M. RANDALL, Rochester, Minn.—The normal hormonal environment responsible for normal endometrial behavior has been fairly well established. A hormonal influence on both normal and abnormal endometrial states is naturally assumed for without the presence of certain steroids this tissue does not proliferate or function. It is quite natural, therefore, to postulate hormonal disturbance or imbalance as the etiological factor of irregular shedding, irregular regression, or prolonged defective desquamation, whichever term you prefer. Brewer and Jones noted that the condition under discussion may occur as a result of functional abnormality of the corpus luteum. The detection of pregnandiol in the urine during the shedding phase by McKelvey and Samuels corroborates this observation. However, Brewer and Jones also noted that a typical regression of the endometrium may occur in the presence of a normally behaving corpus luteum. Their observations were based on cytologic examination which is well known not to be always a completely accurate estimation of function. Nevertheless, those findings do raise the question of whether hormonal influence is solely responsible for the atypical endometrial behavior under discussion and indeed whether irregular shedding may reasonably be called a hormonal or histologic entity. Perhaps it is but part of a more complex upset of endometrial-hormonal relationships. I suspect we may be too prone to accept the endometrium as a tissue always completely responsive to environment and to overlook the probability that the quality and functional capacity of this gland tissue is subject to wide variations. Study of the whole endometrial bed may reveal an atypical picture but not infrequently marked variations occur simultaneously in the same bed—

normal-appearing stages of proliferation or secretion adjacent to areas of marked cystic hyperplasia. It is equally well known that a typical bleeding can occur from any type of normal-appearing endometrium. Also, endometria have misbehaved in the presence of a normal hormonal sequence and balance in so far as we can presently determine by chemical and bioassay.

There is nothing new in this concept but it seems reasonable to emphasize it when one attempts to state that irregular shedding is hormonal or histologic entity—may it not be but part of a whole picture of a disturbed hormonal-endometrial relationship? I believe Dr. McLennan indicates a similar approach to the problem when he states, "It is possible, then, that irregular shedding perpetuates itself and even increases in degree owing to this phenomenon of abnormal vascular retention in the functionalis month after month." May this indicate a primary endometrial defect? I do believe that this condition can be accepted as a clinical entity. The clinical picture and the response to treatment by dilatation and curettage seem established. More general recognition should occur if the criteria enumerated by Dr. McLennan are followed.

DR. EMIL NOVAK, Baltimore, Md.—Dr. McLennan has performed a service in bringing this subject to our attention. It is not an entity which most of you will encounter frequently or recognize for reasons which he has indicated. The histologic pictures which he showed pertain chiefly to hysterectomy cases, but hysterectomy is not frequently done for this condition. We have to base our histologic ideas largely on the appearance of curettings and the curettings reveal usually one variety of so-called mixed endometrium. My experience with this entity is that it is not usually a diffuse picture involving the entire endometrium, but occurs most often in patchy areas, another illustration of the variations in the reactiveness of endometrium to the same hormonal stimulus, a point which Dr. Randall brought out and with which I agree. It is not certain that there is any fundamental endocrine dysfunction, the dysfunction being on the endometrial side. It is not uncommon in studying normal progestational endometria to see large islands of unripe endometrium which have not responded to progesterone. On the other hand, one may see the picture of a postmenstrual endometrium with patches of unshed progestational endometrium on the surface, and it is my impression that it was this picture which was described as "endometritis post-desquamationem" by Driessen in his paper of many years ago to which D. McLennan referred. Whether the patient loses anything important when the condition is not recognized I rather doubt. In most clinics such cases are put down as a variety of functional bleeding, and are probably treated along the usual lines. Indeed, there is no very specific or direct treatment, even if the abnormality is recognized. It is, however, an interesting lesion from the standpoint of hormonal and endometrial interrelationships.

DR. McLENNAN, (Closing).—I am grateful to Dr. Randall and Dr. Novak for their very kind remarks and particularly to Dr. Randall for taking up the subject of the etiology of irregular shedding, which I purposely eliminated from my condensed verbal statement because of its controversial nature and the limitations on my time. Our endeavor in this regard is not to stir up an argument about etiology, but simply to make known more widely the fact that there are patients who have menorrhagia which recurs month after month and which seems to be associated with a retention of unusual endometrial material and which may be corrected by its removal. At the same time one may make a specific diagnosis rather than reach the conclusion that he does not know why the patient was bleeding excessively. We have stressed the desirability of curetting these patients during the bleeding phase, although it is not possible to prove that this is essential for other than diagnostic purposes. Certainly a good many of them must have been curetted at other times in their cycles. Perhaps the end result would be the same, because I am rather convinced that most of the good result is due to removal of the thick-walled arterioles.

With regard to Dr. Novak's comment about the patchiness of the endometrium and the fact that secretory changes are seen with proliferative changes, that is true in certain instances. However, in the vast majority of our specimens the picture has been solely one of retained secretory endometrium but, of course, we have obtained the material as a rule prior to the time any regeneration was undertaken.

I should apologize for using illustrations from hysterectomy specimens, as Dr. Novak pointed out, but I did this deliberately because they are easier for the average person to orient; it is a little simpler to look at such a section than to look at fragmentary curettage material. Obviously the curettage material reveals the same endometrial findings, and these are illustrated in the paper.

THE CAUSE OF DEATH IN PATIENTS TREATED FOR CERVICAL CANCER*

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IN ANALYZING the results of the treatment of cancer the usual approach is to evaluate the number of five-year cures with respect to the various forms of therapy. It was felt that an opposite approach, i.e., an analysis of the *failures* of treatment might reveal equally important information and that is the principal method of attack in this study. Such questions as the following need to be answered: Why do patients die after treatment for cancer? Is it because the growth was too extensive to hope for a curative irradiation response, or a complete surgical removal? Do the patients die because of the local persistence and growth of cancer, or because of lymph node or other metastases? How long do patients live after treatment for cancer? When death occurs *after* five years, is it because of other disease, other cancer, or recurrence of the original disease? If it is recurrence, is death due to persistent local disease or to metastases which were already present at the time of treatment? Can the role of lymph node metastasis be more precisely defined than it now is? Why is it that some patients with "early" lesions die very shortly after treatment and others with "advanced" growth survive for a long period of time? Can deficiencies in treatment explain the early deaths in early cases? The present study cannot begin to answer all of these questions, but posing them helps to indicate the direction of thought.

Material

This study embodies an analysis of the results in the group of patients with cancer of the cervix treated at the University of California Hospital in San Francisco between 1931 and Dec. 31, 1946. The year 1931 was chosen as the starting point because it was at that time that high voltage x-ray therapy became available as a supplement to radium and surgery. Dec. 31, 1946, was chosen as the end point so that a period of observation of at least five years would be available in all instances. During this period, 713 patients were treated, 631 (88.5 per cent) by means of irradiation, and 82 (11.5 per cent) by radical hysterectomy.

The irradiation usually consisted of a combination of radium and x-ray, though in a few early cases radium alone was employed, and in a few hopelessly advanced cases only x-radiation was used. Pelvic lymphadenectomy was performed in 36 of this group in addition to the irradiation. The irradiation plan was as follows:

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Whenever possible, three 50 mg. pieces in tandem were inserted into the cervicouterine canal for a dose of 3,000 mg. hr. Screening: platinum 0.5 mm. (lately 1.0 mm.), rubber 2 mm. The vaginal portion of the cervix was treated by means of an appropriate-sized plaque, sometimes with and sometimes without small bar containers in the lateral vaginal fornices. Fifty and 25 mg. pieces were used for a dose of 1,500 mg. hr. Screening: platinum 0.5 mm., brass 2.00 mm., aluminum 1.0 mm. The total doses were varied upward to 7,000 mg. hr. and downward to 3,500 mg. hr. according to circumstances. For example, if the uterine cavity would accept only two pieces of radium instead of three, the canal dose was reduced one-third. The total doses were usually achieved in two sittings, two weeks apart. X-radiation ordinarily preceded the radium applications and increased over the years from 1,000 r (in air) to each of four fields, two anterior and two posterior, to 3,000 and 4,000 r per field. Both 200 kv. and more recently 800 kv. machines were used.

Radical hysterectomy was reserved for Stage I cases and a few "early" Stages II cases, with due regard for age, general health, obesity, and the like. In not all cases, particularly in the first half of this period, were the regional nodes excised at the time of hysterectomy. Usually one preoperative radium application was given (dose: 1,500 to 3,000 mg. hr.) in order to "clean up" the cervix.

TABLE I. MATERIAL, 1931-1946

STAGE	TOTAL NUMBER TREATED	INCIDENCE (PER CENT)	TREATED RADIOLOGICALLY	TREATED BY HYSTERECTOMY
I	158	22.2	99	59
II	278	38.9	256	22
III	207	29.0	206	1
IV	70	9.9	70	
Total	713		631 (88.5%)	82 (11.5%)

Cause and Time of Death

The cause of death was not possible to ascertain with absolute accuracy in many instances, since it was often necessary to rely upon information obtained from the death certificate, or the word of the attending physician, or a relative. However, in most instances, the patients had been examined in our clinic from a few days to a few months before the terminal event, so that by correlating all of the available information it was possible to arrive at a relatively satisfactory answer. It was frequently not possible, however, to determine whether the patient died wholly on account of the local recurrence of cancer or because of distant metastases or both. The figures should therefore be assessed with these conditions in mind.

TABLE II. DEATHS NOT DUE TO CERVICAL CANCER

CAUSE	DIED IN LESS THAN FIVE YEARS	DIED AFTER SURVIVING FIVE YEARS
Natural causes	28 (2 with cancer)	33
Treatment		
Operation	3	
Radiation	14	
Other cancer	1	4
Total	46	37

To date, 492 of the 713 patients have already died, 83 from causes other than cervical cancer, and 409 because of the cervical cancer. The details of the noncervical cancer deaths are given in Table II.

Two of the patients who died of natural causes in less than five years were known to have cervical cancer still present. Others may also have had their original disease at the time of death, but there was no clinical evidence of it. Five patients died of cancers of other organs, one in less than five years and four after five years. Of these, two had cancer of the stomach, two had cancer of the rectum, and one had cancer of the lung.

The details regarding the 409 deaths from cervical cancer are given in Table III.

TABLE III. CAUSE AND TIME OF DEATH, 409 CERVICAL CANCER DEATHS

STAGE	LOCAL				METASTATIC			
	< 1 YR.	1-5 YR.	> 5 YR.	TOTAL	< 1 YR.	1-5 YR.	> 5 YR.	TOTAL
I	*9*	18	3	*30*	4	8	11	23
II	32	45	5	82	21	33	4	58
III	42	36	1	79	30	38	5	73
IV	30	11	0	41	14	9	0	23
Total	113	110	*9*	232	69	88	*20*	177

TABLE IV. LATE RECURRENCES—OPERATION VS. RADIATION, STAGES I AND II

STAGE	NUMBER	FIVE-YEAR SURVIVORS	PERCENTAGE	RECURRENCES AFTER FIVE YEARS
Radiation.—				
I	99	61	61	11
II	256	110	43	8
Subtotal	355	171	48	19 (11.1%) (10.8% of deaths)
Operation.—				
I	59	48	81	3
II	22	16	73	1
Subtotal	81	64	79	4 (6.3%) (23.5% of deaths)

At least three of these statistics are of interest: (1) There were 30 deaths of patients with Stage I carcinomas apparently due to persistence of the local disease, 9 of them within the first year. These deaths point either to inadequate therapy, where adequate therapy should have been possible, or to a high grade of radioresistance. (2) In the group where deaths were due to metastases, the number of five-year survivors (20) was both absolutely and relatively much greater than in the group succumbing because of the local disease. This was to be expected, I believe, in that we were seeing here the patients whose local disease was relatively well controlled, allowing them to live long enough for the metastases, undoubtedly present from the beginning, to grow and spread farther and finally kill them. A corollary to this observation is that 113, or 48.9 per cent, of the deaths due primarily to persistence of the local disease occurred within the first year, while only 38.9 per cent of the deaths in which metastatic cancer played a leading role occurred within this period. (3) The 29 five-year survivors, who later died of their cervical cancers,

stand out as a warning that the appellation "cure," after five years of freedom from evidence of the disease, is a rather unreliable one. This statistic also suggests that metastasis of any kind, treated or not, carries a very poor prognosis for "cure."

Influence of Type of Treatment

The question of whether the type of treatment influences the incidence of late recurrences is of some interest and importance. For the purpose of illuminating this problem the late results in operatively treated patients were compared with those managed radiologically. It was necessary to confine this comparison to patients with growths classified as Stages I and II. Table IV contains this information.

To put these somewhat confusing figures into meaningful terms I have constructed a hypothetical comparison in Table V, in which the percentages arrived at in Table IV are used to calculate an estimate of expectancy with the two forms of treatment. Let us suppose that we start out with 2,000 Stage I and Stage II cases, distributed as they were in fact in Table IV; if 1,000 of them were treated radiologically and 1,000 were treated operatively, how many would be alive at the end of five years, and of these survivors how many would die of late recurrence after five years? The answers for this hypothetical series are provided in Table V.

TABLE V. LATE RECURRENCE—OPERATION VS. RADIATION, THEORETICAL

TREATMENT	CASES (STAGES I AND II)	WOULD BE ALIVE AT 5 YEARS	WOULD DIE OF RECURRENCE AFTER 5 YEARS
Radiological	1,000	500	50 (1/10 of all cancer deaths)
Operation	1,000	800	50 (1/4 of all cancer deaths)

It would appear that with the treatment provided in this clinic during the period under discussion, the patient who could be treated operatively stood a much better chance (as 8:5) of surviving for five years, and of a longer period of survival after this period than did the patient who was treated radiologically. It is appreciated that the five-year results of radiological treatment reported from some clinics approximate those obtained by operation in this series. It may well be that there were deficiencies in the radiological management of our patients; if so, the deficiencies are not readily apparent. Of more significance in the comparison, I believe, is the greater "permanence" of cure in the operatively treated group.

Additional evidence bearing on this point is the ten-year survival curves (Fig. 1) in which it is seen that there was a much greater salvage of operatively treated patients at the end of five years, than of the radiologically treated, and that the recurrence rate between five and ten years was considerably lower in the former group. In this connection, further inquiry into the nature of the late recurrences is of some interest.

Of the 409 cancer deaths, 33, or 8.1 per cent, occurred more than five years after the initial treatment, 4 of cancer of other organs and 29 of recurrence of

cervical cancer. Of those dying from other cancers, one had a Stage III cancer of the cervix, treated radiologically, and died in the sixth posttreatment year of cancer of the stomach, one originally had a Stage I cancer of the cervix, was treated by means of the Wertheim operation and died of cancer of the rectum in the seventh year after treatment, one with an initial Stage II cancer of the cervix was treated by means of irradiation and pelvic lymphadenectomy and died in the twelfth postoperative year of cancer of the lung, and the fourth patient, whose original diagnosis was Stage IV cervical cancer, died in the tenth year after treatment of cancer of the colon. The late recurrences of cervical cancer are given in tabular form in Table VI.

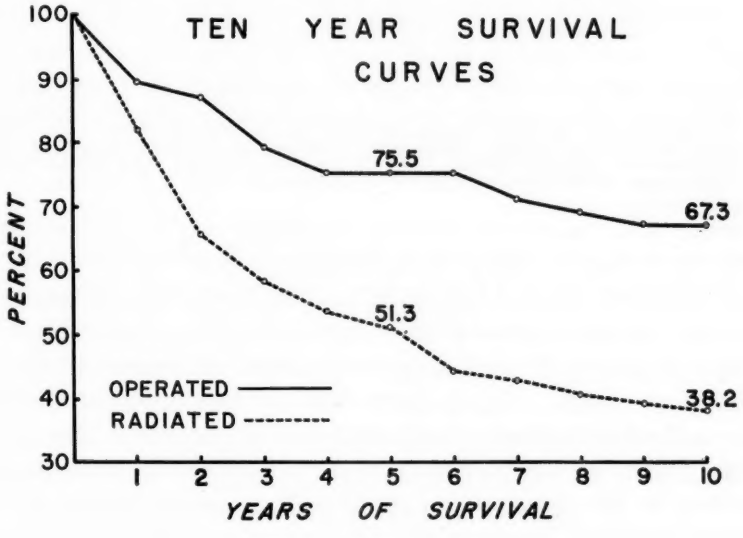

Fig. 1.

While these figures are not large enough to be entirely convincing they appear to show that late recurrences following irradiation were frequently associated with the persistence of the growth in the local tissues, while after operation late recurrences were usually due to metastatic cancer.

Node Involvement

The significance of regional node involvement at the time of initial treatment is of great importance to us from the point of view of prognosis and the aim of future attack. How often it occurs and what can be done about it are questions of the greatest moment. The material under review does not lend itself to an elucidation of the incidence of regional node involvement though there is some information available in the literature regarding this point.

There were 97 cases in which lymphadenectomy was performed, either alone or as a part of the Wertheim procedure during the period under review. In some instances, the operations were preceded by roentgen therapy and not in others, a consideration which need not concern us in this analysis. In 79 instances, no cancer was found in the nodes, while in 18 cases cancer was discovered in one or more of the removed nodes. Twelve of the latter group died

TABLE VI. LATE RECURRENCES

STAGE	YEARS SURVIVED*	TOTAL
Radiation.—		
I	(c c c a c c c c c c a) (8 5 5 5 5 7 8 5 8 7 5)	11
II	(c c b b c c b c) (5 7 5 10 6 10 5 5)	8
III	(c c c b c c) (5 5 9 5 7 5)	6
Operation.—		
I	(d d d) $\left[\frac{d}{\text{plus } 5}\right]$† (6 6 8)	3 [plus 1]†
II	(a) (5)	1
III		
Total		29 (7.1%)

*Figures in parentheses indicate years survived in individual cases. The letters over the figures indicate the type of cancer death: (a) death due to local spread of cancer, (b) death due to local and/or regional spread, (c) death due to local and distant spread, (d) death due to lymph node metastases or distant metastases.

†Recent information.

of cancer and one died as a result of the treatment procedures in less than five years, while 5 survived beyond this period. It is most distressing that only 2 of the 5 five-year survivors are still alive, one at six years and one at fourteen years, the other 3 having died of recurrent metastatic cancer in the interval between five and ten years. The six-year survivor had cancer in a small parametrial node, and the fourteen-year survivor had cancer in one of the obturator nodes. So far as can be determined, none of the 23 patients who died of cervical cancer in less than five years, died of metastatic cancer alone; in all instances cancer recurred locally also. On the other hand, of the 11 deaths after five years, 4 were due to metastatic cancer only, 2 to both local and metastatic cancer, 1 to local cancer only, and 4 were ascribed to causes other than cervical cancer. These results emphasize, as I think it has not been emphasized before, the very serious import of regional node involvement whether or not the nodes are removed. It seems obvious that the removal of involved nodes will not infrequently prolong life, even beyond five years, but it will rarely result in complete and permanent cure. These results dampen our enthusiasm for lymphadenectomy as a therapeutic measure and point to the necessity for a continued search for better methods of dealing with the regional lymphatic tissues in cases of cervical cancer.

TABLE VII. REGIONAL NODES, 97 CASES, 1931-1946

	STAGE	ALIVE	DIED IN < 5 YR.		DIED > 5 YR.		TOTAL
			CA.	OTHER	CA.	OTHER	
Nodes positive for cancer 18	I	1 (6 yr.)	3		3		
	II		9	1			
	III	1 (14 yr.)					
Subtotal		2	12	1	3		18
Nodes negative for cancer 79	I	31	6	1	1	1	
	II	22	4	2	3	1	
	III	4	1			2	
Subtotal		57	11	3	4	4	79

Summary

Death occurs following treatment for cervical cancer because of (1) the local persistence of cancer, (2) regional or distant metastases, (3) a combination of (1) and (2), (4) complications of treatment, (5) natural causes (other than cancer), (6) other cancer. Persistence of local disease is the leading cause of death. Among the late deaths (after five years) metastatic cancer accounts for a greater proportion of the fatalities than it does of those occurring early (before five years). In this series, 9 of the 409 cervical cancer deaths occurred in Stage I cases in less than one year after treatment. It would seem that in these cases either the treatment was markedly deficient, the growths were radioresistant, or there was an error in classification.

The fact that 29, or 7.1 per cent, of the cervical cancer deaths occurred between five and ten years after treatment points to the unreliability of the term "five-year cure." Since there is no certain way of determining cure, it would seem to us to be more sensible to deal entirely in terms of "survivals."

A comparison of the results of surgical treatment and radiological treatment in Stage I and II cases indicated that the chance of surviving for five years was greater after radical surgery than after irradiation. It also showed a longer survival period for the surgically treated patients.

The fate of patients with involvement of the regional nodes, as demonstrated by finding cancer in the removed nodes, was traced. It was found that only 2 of the 18 patients are still alive, though 5 lived for more than five years. It is believed that the seriousness of node involvement, no matter what the form of treatment, has not been fully appreciated.

Discussion

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Morton has called attention to several vitally important factors concerning the cause of death in patients treated for cervical cancer. He has approached the problem by asking a series of pertinent questions that have certainly occurred to all of us in the course of our experience.

Naturally in Stages III and IV patients, and to some extent in Stages I and II patients, the disease fails to respond to the major form of treatment—irradiation—or to surgery as well for that matter, because the disease is either so extensive as to be practically hopeless when first seen or to remain unarrested by treatment because the host for some intangible reason is particularly susceptible to neoplastic influence. It is doubtful indeed whether in such circumstances any treatment or any combination of treatment, i.e., surgery, or surgery and irradiation in combination, would do any better. If this concept be true, it is obvious that local cancer growth goes hand in hand with metastatic manifestations, and it is essentially a matter of incurability rather than a lack of response to treatment.

What terrifies us more, I think, is the case of the patient with a Stage I or early Stage II lesion that responds well to therapy, survives the so-called five-year period, and then develops evidence of metastatic disease through lymphatic spread instead of exhibiting local recurrence. It is this actuality that Dr. Morton stresses in his paper and attempts to solve through his own observations, believing it to be more common in such phases than is local recurrence.

To do this he has relied upon a carefully analyzed series of 82 patients in whom surgery has played a major role in treatment in 11.5 per cent of the 713 patients treated for cervical cancer. I say "major role" because the preliminary irradiation used has been a factor that

cannot be discounted, in my opinion. Hence, it is not a series with an entirely surgical approach, as Dr. Morton frankly states. However, this does not detract from the study, which is one that deals principally with the part that the lymphatics play in cancer dissemination. Lymphadenectomy was also carried out in 36 of the 631 patients treated radiologically, and it would be helpful to know the survival status of these 36 patients included among the 97 reviewed in Table VII, as well as the percentage of involved lymph nodes in this group, especially in view of the varying irradiation factors used.

The selection of patients for hysterectomy was carefully made, and I take it that radium was used preoperatively in all of them. How many of the 82 patients did or did not have regional node dissections is likewise not clear to me. Hence, it is difficult to evaluate in the over-all picture the part that these two factors played: (1) preliminary irradiation with radium, and (2) the number that did have nodal dissections and what the proportion of involved and uninvolved nodes was. Perhaps Dr. Morton can clarify these points, for they may well influence the expressed results and the conclusions drawn.

It is always somewhat difficult to draw conclusions as to patients who apparently die of causes other than cancer within the five-year period, as Dr. Morton states, and the long-term survivors who died of intercurrent or terminal disease not infrequently develop another primary malignancy. Table II is in line with our experiences in the Jefferson Clinic.

I can appreciate Dr. Morton's chagrin with respect to Table III, detailing so meticulously the death record of 409 of the 713 patients treated, for it is an experience many of us share with regard to the 30 Stage I deaths with persistent local disease; we also share in the not uncommon observation of distant metastases later on following a substantially good local result which, in his experience, was absolutely and relatively greater than in those who died of local disease, and this is the crux of his argument. For that reason I agree absolutely with Dr. Morton regarding the employment of the use of the term "five-year cure," which I have never employed in any of the reports from the Jefferson Clinic. We have always used the expressions "survival" or "salvaged"; perhaps the term that I once used—"arrested"—would be even better.

In Table IV we find the comparative data upon which Dr. Morton bases his thesis that long-term metastases are less common in the early case treated by some radium plus surgery as contrasted with similarly staged patients treated solely by irradiation, but while 11.1 per cent of the patients irradiated only exhibited recurrence after five years compared with 6.3 per cent in the group operated upon, the expressed percentage of deaths in the group treated by operation was 23.5 per cent, as compared with 10.8 per cent among the purely irradiated patients. Hence, the number of patients concerned might perhaps be too small upon which to base theoretical Table V. These percentage figures seem to confuse the conclusion that "late recurrences following irradiation were frequently associated with the persistence of the growth in the local tissues, while after operation late recurrences were usually due to metastatic cancer," but this actually means that the majority in the irradiation group show distant as well as local spread, but that a lesser number in the operation group did show local arrest with late remote metastases.

I am tremendously interested in the findings reported in 97 lymphadenectomies performed either alone or as part of the Wertheim procedure or following irradiation alone. In this group of 97 patients, 18.5 per cent had positive nodes, and of these only 2 out of 5 five-year survivors are alive six and fourteen years after operation. Furthermore, of the 79 patients having negative nodes, 14 per cent died within five years. I do not wonder that this experience discourages Dr. Morton with respect to the value of lymphadenectomy, even though the outlook is better percentage-wise if the nodes are negative. I have always wondered how we could draw an inviolate line between removed nodes and the adjacent tissue, or between those lymphatics or nodes beyond reach of the knife with a sense of security and with any certainty that no cancer cells are left behind. Nevertheless, I feel that we should not abandon lymphadenectomy in patients who respond well to complete and planned irradiation therapy—a policy that we are following in the Jefferson Clinic—but an optimum time must be chosen for its accomplishment, if that can actually be done. Otherwise, may we not disturb beneficial fibrotic change induced by irradiation that has literally imprisoned or attenuated cancer

cells? With respect to immediate radical surgery without preoperative irradiation, I still feel that the indications for it must be very closely drawn. A continued observation period must determine our future course with respect to such experimental work in preference to irradiation, either alone or combined with surgery, as represented by subsequent radical hysterectomy with nodal removal or by subsequent bilateral lymphadenectomy.

Our own experience based entirely upon irradiation therapy has been that most of our cancer deaths have been due primarily to retroperitoneal parametrial involvement with ureteral compression and/or invasion resulting in suppression of kidney activity and uremia. A lesser number have died from local disease and hemorrhage, as well as from distant metastases at periods remote from initial treatment; likewise in a few instances from irradiation causes without residual cancer being found at autopsy. This is in line with the earlier findings of Behney and others, and the more recent observations of Henriksen. It is those patients whose disease recurs five to twelve years after apparently successful initial treatment, who in our 1921 to 1946 series amount to about 19 per cent among 463 patients of all stages treated, who point up the need of the thoughtful consideration that Dr. Morton has urged with respect to potential or actual lymphatic involvement and its management. We are certainly indebted to him for his thoughtful and valuable presentation.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—I wish to discuss only one aspect of this paper—the 14 deaths that were ascribed to radiation. During the past three periods of five years each, our survival rate at the Pennsylvania Hospital following radiation for cervical cancer has increased as follows: 28.6 per cent, 39.0 per cent, and 44.8 per cent.

Unfortunately, this improvement in survival rate has been accompanied by an increase in the radiation injuries. Indeed, slightly over 10 per cent of the five-year survivors in the last study group suffered severe crippling radiation reactions. Recently we have undertaken an investigative project that is designed with the hope of increasing the tumor destruction and decreasing the injury to contiguous structures. This effort revolves around determination of the anatomical extent of the tumor and its proximity to other pelvic viscera, individualized planned therapy in terms of optimal tissue dosage pattern, intratherapy study of the geometric distribution and the intensity of radiation, and careful follow-up observation to determine the tumor destruction and the extent of injury to vital structures.

To be more specific, the plan consists of five steps, in the following order: Pretherapy study includes evaluation of the patient as to her general condition and determination of the extent of the neoplasm with identification of associated complications. Following this study the individual problem is reviewed with the radiologists and the general treatment plan is outlined. The second step consists of x-ray therapy during which the parametrium and the associated node-bearing areas are the primary objectives. Central structures, the cervix, the bowel, and bladder, are protected. The size and contour of the patient are measured. Portal roentgenograms, compression techniques, and tumor localization are utilized in order to achieve maximum effectiveness through accurate x-radiation distribution. Through both external and intravaginal portals from 3,000 to 5,000 tissue roentgens are delivered to the parametrium over a period of four to six weeks. A rest period of three to six weeks then follows, depending upon the general response to radiation and the degree of local reaction. The third step consists of re-evaluation as to the response to therapy, the extent of the tumor, the size of the vagina and the uterus, and the microscopic evidence of cellular radiation reaction. Based upon these findings, a tentative plan for the local application of radium is drawn up by consultation between gynecologist, radiologist, and physicist. This plan envisages effective treatment of the primary lesion and supplementary radiation to the parametria and lateral pelvic walls. The fourth step consists of the local application of radium with careful study of the patient while the radium is in place. Prior to the insertion of the radium, radiopaque catheters are placed in the ureters. The technique of radium placement varies between the Regaud principle, the Manchester method, and the Ernst applicator, depending upon many factors such as the size of the upper vagina, the location and extent of the primary lesion, and the proximity of the bladder and rectum. The radium is placed as planned and immediately thereafter roentgenograms are made with radiopaque material in the bladder and in

the rectum. Anteroposterior and lateral films are taken at 90 degree angles to each other from which a three dimensional reconstruction of the important structures may be obtained. If the films reveal poor placement, necessary corrections are made at once. With the distribution of the radiation sources visualized, the tissue dosage is calculated with constant attention to the possibility of injury to the bowel and lower urinary tract. The objective is an even spread of irradiation to all potential tumor-bearing areas so that these zones will receive between 6,000 and 8,000 tissue units by addition of the previously administered x-ray dosage and the gamma roentgens that accrue from the local application of radium. A balance is sought between maximum tumor destruction and minimum effect upon the contiguous vital structures. The fifth step consists of a careful and effective follow-up regimen. Monthly gynecologic examination is done, and at three-month intervals a complete survey of the urinary tract and the lower bowel is carried out. This program has been in effect for approximately two years, and it is our distinct impression that we are destroying more tumor and doing less harm to the contiguous vital structures. Furthermore, the prompt discovery of radiation damage to these structures in its earlier phases enables us to begin therapy that we believe will obviate a considerable proportion of the long-term disabling complications that have been experienced in the past.

This is not a report but rather a preliminary statement of our methods and aims, in the hope that others will join in the effort to strike the narrow line that lies between effective tumor destruction and irreparable injury to the contiguous vital structures.

DR. JOE V. MEIGS, Boston, Mass.—I believe that metastatic carcinoma in lymph nodes or as distant metastases as a cause of death should not be a surprise because the figures presented today are about the same as those found in carcinoma of the breast or any other epithelial malignant neoplasm. On the other hand, two cures at ten years out of eighteen may not seem like much, but if you multiply it by five, it means that ten out of 100 might be surviving today. That is certainly challenging.

We have done about 134 lymph node, retroperitoneal lymph node (Nathanson) dissections up to the present at the Vincent Memorial Hospital. We have no five-year survivals at all. We have 2 four-year survivals, but the ones who have died have had persistent local disease and died probably because they still had tumor shedding off into the lymphatics that we could not control. In Taussig's procedure, which we have done, we have 8 patients with positive nodes and 3 have survived six, eight, and ten years, and I think that is worth thinking about.

I would like to say a word about the work Mrs. Graham is doing on radioresistance or sensitivity. She has taken a comparable group of patients in Grades I, II, III, and IV and considered in her figures the amount of x-ray or radium they have had. She has counted 100 normal cells in the vaginal smear and tabulated the findings of sensitivity in regard to vacuolization of the cell cytoplasm, multiple nuclei, and enlargement or swelling of the cells. She has a series of 76 patients and, in this group, the curability of those that show a satisfactory radiation response is 58 per cent. We would all be grateful for such results. However, in a comparable series who have poor results, only 3 per cent are alive at five years. So it seems that it behooves us all to try to study radiation resistance. Mrs. Graham does her work on the vaginal smear. It would be of great help if we knew which patients to operate upon and which patients to irradiate.

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—The subject of Dr. Morton's paper was the distribution of metastases in carcinoma of the cervix, but it appears to have broadened out into a general discussion of methods of treatment. I am therefore perhaps justified in reporting some work we did five years ago on the relative advantages of radiation therapy and surgical excision with lymph node dissection.

I might begin by expressing my admiration for Dr. McKelvey's methods of statistical control and in particular for his insistence that we must speak about total groups. There is only one weak point in his study, as I see it, and that arises from the possibility that there has been a continual improvement of the clinical material coming for treatment, as the years have passed.

In a short series of cases of cancer of the cervix treated in 1945-1946 by Dr. Gray Twombly and myself at the Memorial Hospital, we believe we eliminated this possible source of error by treating alternate patients by the methods to be compared. The two groups, of about 40 patients each, contained cases of Stages I and II and were as nearly identical as possible. Dr. Twombly has recently compiled the results and will present them at a meeting of the American Radium Society. The radiation series had a cure rate of 71 per cent, and the surgical series of about 60 per cent. This difference is not statistically conclusive in a series of this size.

It should furthermore be noted that in the cases originally referred by the plan to surgery, twelve were regarded as inoperable, for medical or technical reasons, and were treated by radiation. The results in this segment of the "surgical" series were very bad. If these cases that were not operated upon be subtracted from the "surgical" series, the results of those actually having a radical operation became 80 per cent. This figure shows how surgical therapy may yield apparently superior results because of a selection which eliminates particularly the cases with a bad outlook.

It appears impossible at the present time to arrive by statistical means at a final conclusion as to which method is preferable. It seems essential that both methods continue to be studied and compared with as little preconceived prejudice as possible.

DR. CHARLES A. BEHNEY, Los Alamos, N. M.—The discouraging experience of Dr. Morton, in the persistence of carcinoma in early cases of cervical cancer despite adequate therapy, is one that all of us share. Some tumors appear to be resistant to the maximum amount of irradiation that can be given safely with methods presently available. Such neoplasms can be recognized by following the practice suggested by Meigs, in taking postirradiation biopsies and smears. These readily demonstrate whether or not the therapy is proving lethal to the tumor cells.

Those of us who believe that there is a place for radical surgery in the treatment of carcinoma of the cervix have found it advantageous to select for radical hysterectomy those patients in whom repeat biopsies and smears failed to show a satisfactory radiation effect on the tumor cells. Fortunately, these are the tumors that are in most cases less likely to have early metatases.

Table I was prepared from the literature on this subject since 1933, and is based on observations made at autopsies of patients who died from cancer of the cervix.

TABLE I. CAUSES OF DEATH FROM CARCINOMA OF THE CERVIX (COLLECTED FROM THE LITERATURE SINCE 1933)

AUTHOR	NO. OF CASES	RENAL DISEASES*	PERITONEAL SEPSIS†	HEMORRHAGE	PULMONARY‡ DISEASES	SEPTICEMIA	BOWEL OBSTRUCTION	CACHEXIA, ETC.	UNRELATED DISEASE
De Alvarez	55	40%	9%	2%	31%	0	9%	3%	6%
Pearson	57	33%	19%	9%	3.5%	0	14%	12%	10%
Brunschwig and Pierce	65	27.7%	27.7%	?	?	11%	3.1%	?	?
Auster and Sala	124	28%	28%	8%	8%	23%	1%	3%	1%
Behney	166	21%	3%	9%	26%	9%	6%	22%	4%
Total and average	467	28%	15%	8%	18%	11%	5%	12%	3%

*Uremia and/or pyelonephritis.
†Includes pelvic abcess.
‡Includes septic pneumonia.

It is interesting to note that the more recent reports, since antibiotics have been available, ascribe fewer deaths to infectious processes. There is likewise a smaller number of deaths attributed to cachexia. In the light of our present knowledge of radiation tolerance, I am convinced that many of the latter diagnoses were in reality deaths from overirradiation.

Dr. Morton's Table IV demonstrates the fact that the frequency of distant metastases in Stages I and II increases, roughly, in proportion to the time the patient survives her initial

treatment. This observation has been made by de Alvarez and coincides with our own experience. Patients must live a certain period of time, after the onset of the disease, before distant metastases can grow to recognizable size. As surgical and radiological techniques improve, we must expect to find a greater number of metastases beyond the pelvis.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—I believe that it is about time that we went on record as admitting that certain radiation injuries are permissible in the far-advanced tumors that we are called upon to treat, and that we must accept such injuries as we accept the surgical removal of those organs that are invaded.

As to Dr. Taylor's comments, if he was in error in five cases in the operable group, he was also in error in five cases in the irradiation group and he cannot afford to delete cases from one group without deleting from the other.

DR. MORTON (Closing).—I wish to say that this series of cases was not analyzed with the idea of attempting to evaluate the various methods of treatment and, therefore, some details regarding the series are lacking. However, I can make some additional comments.

In the first place, the five-year survival rate for the 713 cases was 40.8 per cent, which we feel is fairly well in line with what seems to be possible today. With regard to the number of hysterectomies which were done in which lymphadenectomy was part of the operation, I may say that in the earlier part of this series hysterectomy was done without lymph node dissection in a fairly large proportion. For the group of cases considered, 57 of the 82 had lymph node resections and 25 did not. Of the 57 who had lymph node resection and hysterectomy, 38 are living and 19 are dead, although 6 of these 19 lived for five years; 3 had positive nodes and 3 negative nodes. There were 36 lymphadenectomies alone; 17 of these patients survived five years and are still alive, one from whom a positive node was removed. Three five-year survivors in this group died of carcinoma after five years. In this little group of 36 there were 8 with positive nodes, of whom 7 died in less than five years and one patient is still living.

In connection with the results of hysterectomy, Dr. Scheffey mentioned preoperative radiation and feels that it may have had an effect on the results. I think that is entirely possible though the doses were quite small. However, I believe that preoperative irradiation is often indicated and has a very distinct place. I refer especially to cases with bulky tumors which are still confined to the cervix—cauliflower-like masses; I believe that there is a hazard in performing an operation in such cases. I think that in such instances the chance of seeding the carcinoma is materially greater and, therefore, it might be wise to treat the patient sufficiently by means of radium to get rid of the local cervical growth before operating.

I agree with Dr. Schmitz and Dr. Behney that we pay a price for good irradiation therapy. If we are going to give effective radiation, we are bound to have difficulties, yet as soon as we start to reduce the dose very much, our percentage of cures goes down. This does not mean that we cannot have some improvement in methods, such as Dr. Payne has described, an effort which I think is excellent.

A CLINICAL EVALUATION OF THE USE OF RADIUM THERAPY IN THE CONTROL OF BENIGN UTERINE BLEEDING*

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SINCE its introduction into gynecologic practice about forty years ago, radium has been regarded as a satisfactory means of treating benign uterine bleeding. Although certain defects and inadequacies of the method have been recognized, its wide utilization has not been seriously challenged until recent years. In 1936 Norris and Behney[5] stated before this Society that "radium irradiation is now generally accepted as the method of choice in the treatment of certain types of uterine hemorrhage of benign origin." Their paper which reported 1.09 per cent of carcinoma of the genital tract in the patients followed and the subsequent discussion did not seriously challenge the validity of their opening statement although Eardley Holland of London raised the question as to whether or not radium in the uterus has any effect in promoting the incidence of cancer of the body of the uterus. Pemberton reported upon four patients who developed pelvic malignancy among 425 patients treated and followed for two or more years. Since then, a number of papers[1-10] have appeared which have called attention to the subsequent development of cancer principally of endometrial origin in patients who have been treated with radium for uterine bleeding of benign origin. These reports have aroused quite a bit of controversy with respect to the wisdom of this procedure. A few similar experiences have prompted us to undertake an evaluation of our own results with this method which has been the accepted practice in The Division of Gynecology, Department of Obstetrics and Gynecology of The Jefferson Medical College and Hospital.

Our material consists of the case records of 1,232 patients treated from 1930 to 1950, inclusive, this period being chosen because of the greater validity of the follow-up records. Four hundred sixty-five were ward patients and 767 were treated on the private service. All of the patients complained of abnormal bleeding. One hundred seventy-six of these had symptoms referable to pelvic floor relaxations which were corrected by appropriate vaginal plastic procedures at the time of the radium application. Careful pelvic examination under anesthesia, thorough diagnostic curettage specifically directed toward scraping the entire surface, particularly the cornual areas, and the cervical canal, together with cervical biopsy in appropriate instances, was customary in every case.

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

In general, the indication for treatment was abnormal bleeding in women approaching or in the menopause in whom expectant treatment had failed, and in whom no extrauterine lesion could be demonstrated. Among those with myomas, radium was restricted in most cases to intramural tumors with a mobile uterine fundus not larger than a three months' pregnancy.

Definite contraindications were fever, leukocytosis, rapid blood sedimentation (out of proportion to associated anemia), pelvic pain or pressure, adnexal disease, pedunculated, submucous, soft or tender myomas, and fear of radium. Whenever possible, irradiation has been avoided in highly nervous women. In some instances, irradiation has been used when the indications were not ideal, but where hysterectomy was deemed unwise for one reason or another. This group includes a few patients whose myomas were larger than a three months' pregnancy, and some who were under 40 years of age.

Previous to 1937 irradiation was administered by means of two 50 mg. capsules of radium sulfate enclosed in glass, one screened with 0.3 mm. of silver and 1.0 mm. of brass and the other with 0.5 mm. of platinum. Since 1937 the capsules have been screened with 1.5 mm. of platinum. During the past two years, multiple small source units of 5 mg. each, screened with 0.5 mm. of platinum have been used in all patients whose bleeding history has been suggestive of endometrial cancer, the ultimate dose depending upon the four-hour report from the pathologist obtained from the curettage at the time the radium was inserted. Of the entire group of 1,232 patients, 851, or 69.2 per cent, have been followed by examination or questionnaire for six months to twenty-one years. Those followed for less than six months are listed as not followed. The result of treatment is evaluated as satisfactory or unsatisfactory according to whether or not the bleeding has been controlled. Patients who have had a second curettage incident to slight bleeding often following estrogen therapy are not regarded as having unsatisfactory results unless further radiation or surgery has been necessary.

We have not used the severity of menopausal or vasomotor symptoms in our evaluation of therapy. In our experience, the irradiation menopause has not often been more severe than the surgical menopause. The difficulty of accurately interpreting such symptoms without bias is well known and our experience in this respect does not differ from that of others. As a matter of interest, among 399 patients who complained specifically of hot flushes, 70, or 17.6 per cent, described them as severe. These patients were rather evenly distributed among the ages 40 to 49 years, a few were over 50, a time when such complaints are not rare in women generally. Only 7 women stated that they had been seriously ill or incapacitated as a result of the radium menopause. Two of these were 48 years of age and 5 were 50 or more when treated. This does not seem to be a greater number than one would expect to encounter in an equal number of apparently normal women.

The cases have been divided into two groups, dysfunctional bleeding and myomas (Table I). The former group includes those patients in whom the clinical diagnosis was dysfunctional bleeding, chronic metritis, fibrosis uteri,

or metropathia hemorrhagica. The diagnosis of dysfunctional bleeding was made usually when the uterus showed little or no enlargement. In the others, it was often as large as a six or eight weeks' gestation.

TABLE I. RADIUM THERAPY IN THE CONTROL OF BENIGN UTERINE BLEEDING, PATIENTS TREATED, 1930-1950

Dysfunctional bleeding	776		
Follow-up		526	67.9 per cent
Myomas	456		
Follow-up		325	71.1 per cent
Total	1,232	851	69.2 per cent

In the dysfunctional group, the over-all results were satisfactory in 93.1 per cent of the patients (Table II). In the younger age groups the results are generally less satisfactory. Undoubtedly this is due to the lesser irradiation often used in some patients, in cases where the objective was correction and not complete abolition of the menses, and also probably due to the fact that the ovary of the younger patient has greater recuperative power. Table III reveals that many patients received 1,000 mg. hr. of radium or less. Few received more than 1,500. The satisfactory result in the low-dosage group is undoubtedly due to the fact that 600 mg. hr. of radium proved adequate in older women with small uteri. The failures were mostly in younger women who received the smaller doses. Six failures among 38 patients, in the dosage range of 1,500 to 2,000 mg. hr., is not a true index of the over-all effectiveness of the dosage in this group. One of these patients had leukemia which probably influenced recurrence of bleeding, and in 3 others the presence or absence of quite small submucous myomas was debatable. Since this was not actually confirmed, the original diagnosis of fibrosis uteri has not been changed.

TABLE II. DYSFUNCTIONAL BLEEDING, RESULTS IN RELATION TO AGE GROUP, 526 PATIENTS FOLLOWED, 67.9 PER CENT

AGE GROUP (YEARS)	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
35-39	36	29	80.6	7
40-44	114	104	91.2	10
45-49	201	191		10
50-54	117	113		4
55-59	44	41		3
60 or older	14	12		2
Total	526	490	93.1	36 6.9 per cent

TABLE III. DYSFUNCTIONAL BLEEDING, RESULTS IN RELATION TO DOSAGE, 526 PATIENTS FOLLOWED, 67.9 PER CENT

MG. HR. DOSAGE	PATIENTS	SATISFACTORY	PER CENT	UNSATISFACTORY
300- 600	27	25	92.6	2
600-1,000	160	144	90.0	16
1,000-1,500	256	244		12
1,500-2,000	38	32		6
2,000-2,500	36	36		0
2,500 or more	9	9		0
Total	526	490	93.1	36 6.9 per cent

Table IV shows that 30 of the 36 failures in the dysfunctional group occurred during the first five years of follow-up and 15 of these during the first two years. The six failures that occurred in the 257 patients followed from five to twenty years were due to subsequent malignancy.

TABLE IV. DYSFUNCTIONAL BLEEDING, RESULTS IN RELATION TO DURATION OF FOLLOW-UP, 526 PATIENTS FOLLOWED, 67.9 PER CENT

DURATION PERIOD IN YEARS	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
½ to 2	132	117	88.6	15
2 to 3	40	35	87.5	5
3 to 5	97	87		10
5 to 10	158	154		4
10 to 20	99	97		2
Total	526	490	93.1	36 6.9 per cent

Table V shows that 19 of the 36 patients whose initial result was unsatisfactory were reirradiated. The results in 16 of these have been satisfactory and in one unsatisfactory. Two have not been followed. Hysterectomy was performed in 14 of the 36 of whom 13 are living and well; one died several years later of cancer of the corpus, following detection and treatment of the lesion. Abdominal exploration was done in two patients with advanced malignancy, one of whom had cancer of the corpus, while the other developed a primary cancer of the ovary. Both are dead. One patient refused treatment and has not been followed. Six of the 36 unsatisfactory results were due to malignancy, 5 originating in the corpus and one in the ovary.

TABLE V. DYSFUNCTIONAL BLEEDING, UNSATISFACTORY RESULTS, 526 PATIENTS FOLLOWED, 67.9 PER CENT

PATIENTS	PER CENT	SUBSEQUENT MANAGEMENT		END RESULT	
36	6.9	Reirradiation	19	Satisfactory	16
				Unsatisfactory	1
				Not followed	2
		Hysterectomy	14	Satisfactory	13
				Dead of carcinoma	1
		Exploration	2	Dead	2
		Refused treatment	1	Not followed	1

Cancer of corpus in 5 patients, 2 dead
Cancer of the ovary in 1 patient, dead

In the myoma group (Table VI) 325, or 71.1 per cent of the 456 patients treated, have been followed from six months to twenty-one years. The result has been satisfactory in 284, or 87.4 per cent, and unsatisfactory in 41, or 12.6 per cent. The relatively large number of failures in the younger age group is perhaps due (as in the dysfunctional group) to the smaller doses usually used in these patients as will be seen in Table VII which shows only 74.5 satisfactory results in the low-dosage groups. When studied in relation to the duration of the follow-up (Table VIII) it will be seen that a substantial number of the failures occurred within two years and a large majority within

three years of the initial treatment. Although the number of failures in the later follow-up years is small, 6 of the 7 were due to the subsequent development of carcinoma.

TABLE VI. BLEEDING ASSOCIATED WITH MYOMAS, RESULTS IN RELATION TO AGE GROUPS, 325 PATIENTS FOLLOWED, 71.1 PER CENT

AGE GROUP (YEARS)	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
35 to 39	25	18	72	7
40 to 44	85	69	81.2	16
45 to 49	133	123		10
50 to 54	64	59		5
55 to 59	15	13		2
60 or older	3	2		1
	325	284	87.4	41 12.6 per cent

TABLE VII. BLEEDING ASSOCIATED WITH MYOMAS, RESULTS IN RELATION TO DOSAGE, 325 PATIENTS FOLLOWED, 71.1 PER CENT

MG. HR. DOSAGE	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
300 to 600	12	8		4
600 to 1,000	47	35	74.5	12
1,000 to 1,500	160	143	89.4	17
1,500 to 2,000	40	38		2
2,000 to 2,500	56	51		5
2,500 or more	10	9		1
Total	325	284	87.4	41 12.6 per cent

TABLE VIII. BLEEDING ASSOCIATED WITH MYOMAS, RESULTS IN RELATION TO DURATION OF FOLLOW-UP, 325 PATIENTS FOLLOWED, 71.1 PER CENT

DURATION PERIOD IN YEARS	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
½ to 2	48	30	62.5	18
2 to 3	39	29	74.3	10
3 to 5	55	49		6
5 to 10	84	82		2
10 to 20	99	94		5
Total	325	284	87.4	41 12.6 per cent

Results in relation to the size of the uterus are dependent upon the accuracy of original interpretation and evaluation when the patient was examined under anesthesia. This must vary considerably with different examiners. Table IX indicates little difference in results in patients whose uteri varied in size from less than six to twelve weeks' gestation. A much larger proportion of the failures (30 per cent) are found in the uteri of twelve weeks' gestation or larger. These failures are probably a true index of what may be expected from intrauterine radiation in tumors of this size. On the other hand, 6 satisfactory results in patients with uteri estimated to be as large as sixteen weeks' gestation indicates that even some patients with tumors of this size can be thus treated satisfactorily.

Table X reveals that in 41 patients with myomas the initial treatment was not satisfactory. Nineteen were reirradiated and in 13 the final result was satisfactory. Of 3 patients in whom it was unsatisfactory, two developed

cancer of the cervix and one refused further treatment. The other 3 were not followed. Hysterectomy was finally performed in 21, with satisfactory result in 18. Two of the 3 with unsatisfactory results died of cancer of the corpus and one was not followed. Additionally, one patient developed pyometra and has been well since it was drained. Four of the 41 failures in the myoma group were due to developing cancer of the corpus and two developed cancer of the cervix.

TABLE IX. BLEEDING ASSOCIATED WITH MYOMAS, RESULTS IN RELATION TO UTERINE ENLARGEMENT, 325 PATIENTS FOLLOWED, 71.1 PER CENT

COMPARISON WEEKS OF GESTATION	PATIENTS	SATISFACTORY	PERCENTAGE	UNSATISFACTORY
6 or less	112	102	91.1	10
6-12	170	152	89.4	18
12-16	31	21		10
16 or more	6	6		0
Unknown	6	3		3
Total	**325**	**284**	**87.4**	**41 12.6 per cent**

TABLE X. BLEEDING ASSOCIATED WITH MYOMAS, UNSATISFACTORY RESULTS, 325 PATIENTS FOLLOWED, 71.1 PER CENT

41 PATIENTS—13 PER CENT				
TREATMENT		END RESULT		
Reirradiation	19	Satisfactory	13	
		Unsatisfactory	3	
		Cancer of cervix		2
		Refused treatment		1
		Not followed	3	
Hysterectomy	21	Satisfactory	18	
		Unsatisfactory	2	
		Dead, cancer of corpus		2
		Not followed	1	
Drainage of pyometra	1			
		Cancer of corpus in 4 patients		
		Cancer of cervix in 2 patients		

Table XI tabulates the histologic diagnoses of the endometrium in the entire group of 1,232 patients treated, and agrees with the generally accepted concept that abnormal uterine bleeding may occur from endometria of any type. The secretory phase was noted in 129 and the proliferative phase in 209 patients in the dysfunctional group, and hyperplasia in some form occurred in 324. If those instances in which no endometrium could be secured are included as atrophic, it will be noted that 97 patients in the dysfunctional group bled from an endometrium of this type. In the myoma group, the various types occur in essentially the same relative proportions. It is interesting to note that 198 patients with myomas bled from a hyperplastic endometrium, indicating that this associated functional disturbance is probably a factor that influences the bleeding in this group.

No one type of endometrium predominated among the patients whose initial treatment was unsatisfactory. Among these, secretory endometria

occurred 14 times, proliferative 24, hyperplastic 31, and atrophic 6 times. In two, the original endometrial diagnosis was unknown. Twenty of the 31 hyperplastic endometria occurred among the failures in the myoma group. In the patients who eventually developed cancer of the endometrium, the original endometrium revealed atrophic changes in 3, mild cystic hyperplasia in 3—one of which was localized in a proliferating endometrium, "carcinoid" hyperplasia in one, proliferative phase in one, and secretory phase in one.

TABLE XI. ENDOMETRIAL FINDINGS

PHASE	DYSFUNCTIONAL BLEEDING PATIENTS TREATED	BLEEDING WITH MYOMAS PATIENTS TREATED
Secretory	129	77
Proliferative	209	106
Hyperplastic	324	198
Atrophic	59	28
No curettings	38	41
Unavailable	17	6
Total	776	456

Pelvic malignancy developed subsequently in 12 of the 851 patients followed (Table XII), representing an incidence for the entire series of 1.4 per cent. These were divided equally between the dysfunctional and the myoma groups. In the dysfunctional group, 5 cancers of the corpus developed, six, eight, eleven, twelve, and fifteen years after the initial irradiation. The endometrium at the time of original treatment showed atrophic endometrium in one, cystic hyperplasia in one, local hyperplasia in proliferating endometrium in one, atrophic endometrium in one, and premenstrual endometrium in one. The latter patient subsequently bled from a hyperplastic endometrium 7 years after the original treatment and five years later was found to have adenocarcinoma. The irradiation dosage was 800, 1,200, 1,200, 1,800, 300 mg. hr. with a second dose of 400 mg. hr. after a lapse of seven years in the latter patient. One advanced cancer of the ovary occurred eight years after the original treatment in a patient who had never returned for follow-up examination after one year and was operated upon elsewhere because of an abdominal tumor. No cancer was found in the uterus. Thus 6 cancers developed in the dysfunctional group, making an incidence of 1.14 per cent.

TABLE XII. SUBSEQUENT PELVIC MALIGNANCY, 851 PATIENTS FOLLOWED, 69.2 PER CENT

	526 PATIENTS IN DYSFUNCTIONAL GROUP		325 PATIENTS IN MYOMAS GROUP	
Cancer of cervix	0	0.0%	2	0.6%
Cancer of corpus	5	0.95%	4	1.2%
Cancer of ovary	1	0.19%	0	0.0%
Total	6	1.14%	6	1.8%

Among the 325 patients in the myoma group, 6 developed cancer subsequently, 4 in the corpus and 2 in the cervix, or 1.8 per cent. One of the corpus cancers was found unexpectedly on examining the endometrial cavity following hysterectomy for a submucous myoma one year after the initial treat-

ment. The lesion, which was about 2 cm. in diameter, was high in the endometrial cavity and probably inaccessible to the curette originally because of the distorted endometrial cavity which was not appreciated. This lesion was probably present originally. The other corpus cancers occurred four, ten, and eleven years following the original irradiation. The original enodmetrium in these patients revealed slight hyperplasia, carcinoid hyperplasia, proliferative phase, and atrophic changes, respectively. The cervical cancers occurred eleven and eighteen years after the radium treatment.

Comments and Conclusions

In our study of the entire group of 851 patients who have been followed, we have been impressed by the fact that 90 per cent of them have expressed satisfaction with the result of the treatment and for their subsequent good health. This is an impressive figure. More radical treatment would not have been justified, in these women. Evaluation of this method of treatment should not be based solely upon an appraisal of the small minority of unsatisfactory results which have been commented upon in the text. If the number of failures can be further reduced by restricted criteria for its indication and by rigid adherence to them, then irradiation with radium may well continue to be an acceptable method of treatment for benign uterine hemorrhage.

Fear of cancer on the part of the patient and on the part of the physician has become an important factor in restricting the use of irradiation and increasing hysterectomy. This anxiety has led to a certain amount of condemnation of the method following the discovery of cancer in some patients subsequent to irradiation for benign conditions, often because of errors in diagnosis and judgment, while the beneficial results in properly selected cases have not been stressed sufficiently. This has been the real reason for this presentation. The incidence of subsequent cancer in our series is 1.4 per cent. Certainly the frequency of surgical errors in the diagnosis and management of uterine cancer especially of the corpus would substantially exceed this figure, as has been brought out in the work of The Committee for the Study of the Delay Period in Pelvic Cancer carried out in Philadelphia during the past six years.

If radium irradiation is to be satisfactory, it must be repeated that every precaution ought to be taken to insure accuracy of diagnosis primarily. Every patient in whom the indications are not clearly defined should be excluded from such therapy. Although, in our experience, symptoms of irradiation menopause have not been a prominent factor, in most instances emotionally unstable women are poor subjects for irradiation therapy. Adequate irradiation dosage is a very necessary factor in securing a satisfactory result. Twelve hundred mg. hr. or less has sometimes been inadequate. Fifteen hundred mg. hr. is probably a more optimum dose with some variation depending upon the size of the uterus and the relationship of the ovaries to the source of the irradiation. In our experience there has been no evidence to indicate that irradiation per se has increased the incidence of cancer as was pointed out by Scheffey[7] in his presentation before this Society in 1942. Physicians and pa-

tients alike should also recognize the importance of an adequate follow-up examination if irradiation therapy in the treatment of benign uterine bleeding is to achieve full success.

The authors wish to express their thanks to Professor Lewis C. Scheffey, Head of the Department of Obstetrics and Gynecology and to Professor Peter A. Herbut, Head of the Department of Pathology, for their cooperation and assistance in carrying out this study.

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Discussion

DR. WILLIAM P. HEALY, New York, N. Y.—As the author says, the intrauterine use of radium in women of menopausal or premenopausal age for the control of benign bleeding from small uterine myomas and so-called dysfunctional hemorrhage has been found for many years to be a simple, safe, and satisfactory procedure.

On the other hand, there is no doubt that the present low mortality from total hysterectomy in these simple uncomplicated cases threatens to lead some gynecologists who are fully competent to administer radium therapy to advise or encourage these patients instead to undergo hysterectomy.

It seems to me the one and only outstanding indication for hysterectomy in these uncomplicated cases is in the younger woman who appears to have normally functioning ovaries in order to permit their retention and thereby avoid the annoying symptoms likely to follow radiation castration in such women.

The subject is one which in recent years has created considerable interest from different angles. The author has given us a splendid actual report of his experience and that of his associates in the treatment of a large number of these patients over a period of twenty years. It should go far toward clearing up a number of moot points.

For thirty years or more radium in the form of intrauterine capsules has been used very freely by some of us for the control of excessive uterine bleeding, especially before or during the climacteric and in the absence of other uterine lesions except small nonpedunculated fibromyomas not exceeding the size of an eight to ten weeks' gestation. From time to time in an individual case we have been disappointed because of some coincident or post-radiation complication such as an annoying but temporary leukorrhea or a rather late radiation cystitis. Rarely after some months a patient might have excessive involutional changes in the vaginal and vulval mucous membranes and tissues resulting in dyspareunia which would require endocrine therapy. Occasionally the treatment fails to control the bleeding and it has to be repeated or a total hysterectomy may be done. Some patients we know because of a fear of radium do not fit into the radiation picture but on the other hand there are others who dread the mutilation and risk of major surgery for a condition which they regard as relatively minor but do accept willingly the lesser surgical procedure associated with curettage and the introduction of radium capsules. Actually in some cases the diagnostic curettage is sufficient to control the bleeding.

Regarding the choice of cases, I agree with the author that in the presence of extensive glandular hyperplasia hysterectomy may be preferable if not otherwise contrain-

dicated. It also seems to me in the presence of submucous and/or multiple intramural fibromyomas hysterectomy is superior to irradiation. The reasons for this are that we are already dealing with a tumor-bearing organ, 38 per cent of our cases of endometrial cancer were associated with fibromyomas, and endometrial hyperplasia often is coincident with fibromyomas.

Since endometrial carcinoma is essentially a postmenopausal disease it is evident the older the patient the greater the chance of carcinoma instead of a benign lesion being the cause of the bleeding. Therefore, it would seem the older the patient the greater might be the indication for hysterectomy.

It is always understood that in each case under consideration for intrauterine radium therapy a careful diagnostic evaluation of the entire patient including curettage and a histopathologic report will be made before treatment is given. This will diminish the chance of error or of making a bad choice of patient.

As regards radium dosage, there seems to be a tendency to give 1,500 to 1,800 mg. hr. or more with a so-called fibroid tandem applicator filtered with the equivalent of 2 mm. of brass. I believe this dosage in a uterus of average size should be ample to establish castration and should threaten little radiation damage to the uterus or adjoining viscera. If a greater dose is to be given I prefer to have a large uterus and more capsules so as to distribute the radiation over a larger field. If this treatment fails to control the bleeding I would not repeat it in less than six months. However, at that time in the presence of a primary radiation failure if bleeding still persisted I would prefer hysterectomy if feasible. Such a failure I think is more likely to be due to adenomyosis rather than inadequate radiation.

A serious question is the possible relationship between these treatments with radium and the appearance in later years of a malignant tumor, cancer or sarcoma, in some of these uteri. A careful evaluation of the reports bearing on this question would seem to indicate that the incidence is little if any greater as regards cancer than would be normally expected. Certainly it would be stretching the imagination too far to ascribe the occasional case of cancer of the cervix to the use of radiant energy in the corpus years before.

The reports of endometrial carcinoma developing years later when carefully studied seem not to exceed 1 per cent which is fair enough when one considers the rather broad indications which have been used over the years in choosing cases for treatment. No doubt errors of selection have been made in the past which will not be made in the future.

Sarcoma of the uterus as a postradiation complication is more difficult to explain. However, there is no sound reason to believe that the dose of radium energy given in these cases would have a sarcomagenic effect.

Finally, it would appear that the actual incidence of malignant tumors of the corpus as a late complication following intrauterine radium therapy for benign bleeding is too infrequent and questionable to be advanced as an argument in favor of hysterectomy over radiation as the treatment for this symptom.

DR. MONTGOMERY (Closing).—I want to thank Dr. Healy for his discussion and for the very clear way in which he has emphasized many points about which we are in complete agreement.

Original Communications

THE PLACE OF THE HYDRAZINOPHTHALAZINE AND THIOPHANIUM COMPOUNDS IN THE MANAGEMENT OF HYPERTENSIVE COMPLICATIONS OF PREGNANCY

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During the past few years, a great deal of physiologic reinterpretation has been introduced in our concept of the pathogenesis of arterial hypertension.[1-5] This reinterpretation has been mostly due to the development of new agents and techniques which served as physiologic tools in the study of hemodynamic regulations in health and disease. It is now well appreciated that increase in the peripheral resistance and elevation of the blood pressure can be caused by a multiplicity of factors, which can act through either increase in neurogenic impulses or humoral mechanisms or both, provided the intrinsic factors which regulate the receptivity of the vessel walls remain constant. Consequently, in the proper management of a hypertensive state, the causes as well as the mechanisms producing the blood pressure elevation should be thoroughly evaluated.

In pregnancy, hypertension is not infrequently found, either as part of the syndrome peculiar to gestation called acute toxemia, or as a part of chronic cardiovascular or renal diseases associated with pregnancy. From the clinical and prognostic viewpoints, it is important to differentiate between these entities—a task which frequently presents enormous difficulties, particularly when the history is not clear and the patient is seen for the first time with the illness already developed. The problem is further complicated by the fact that very often during pregnancy acute toxemia may become superimposed on a pre-existing chronic hypertensive condition. From the standpoint of management, such differentiation is likewise valuable, since the available evidence tends to indicate that each one of these hypertensive states responds differently to the action of vasodepressor drugs.[1-10] This difference in response has led to the development of a large number of specific pharmacologic agents aimed to produce vasodilatation and reduce the blood pressure without affecting the blood volume or any other vital organs of the body. Some of these agents have a well-established pharmacodynamic action; among these are the autonomic and adrenergic blocking drugs.[11] Others have definite vasodepressor activities, but the site of action is as yet not well understood.

The object of the present report is to discuss two vasodepressor substances which have recently received a great deal of attention in the medical literature, particularly that related to the field of hypertension.

The Hydrazinophthalazine Compounds

Gross, Druey, and Meier[12] were the first to discover, in animals, that a series of synthetic compounds of the phthalazine group has distinct hypotensive activities. These authors found that a remarkably long-lasting vasodepressor effect concomitant with a rise in the pulse rate and increase in coronary and renal blood flows can be achieved with these drugs. Shortly thereafter, numerous investigators in this country and abroad undertook experimental works in a variety of animals with the aim of studying the pharmacodynamic properties of these compounds.[13-21] The compound which has received more attention is 1-hydrazinophthalazine, known commercially as Apresoline.* Practically all the investigators who have worked with this drug agree that, in animals, a single dose given intravenously, intramuscularly, or orally, produces a fall in the blood pressure lasting from 3 to 6 hours. There is usually a latent period of 5 to 15 minutes following the intravenous injection, but thereafter the blood pressure progressively falls, the diastolic prior to and more markedly than the systolic. This vasodepressor effect is observed in widely differing forms of hypertension and even after total sympathectomy. The hypotensive activity of Apresoline can be partially counteracted by epinephrine or norepinephrine either in single doses or by intravenous drip.

One interesting property of this drug is its effect on the renal blood flow. The original observations of Gross and his co-workers[12] which were performed in the rabbit with the use of a thermostromhur showed a significant increase in renal blood flow. Moyer and his associates,[20, 21] using the clearance and renal vein catheterization techniques in unanesthetized dogs, found increase in renal plasma flow and decrease in the glomerular filtration rate. The urine volume was somewhat reduced. In anesthetized animals, their findings consisted mostly of reduction in renal blood flow and filtration rate.

The site of action of these compounds is as yet not well determined. The current hypothesis is that Apresoline acts centrally on the vasomotor centers and on certain areas of the midbrain. It has also been suggested that it might counteract some circulating hypertensive substances. Moderate adrenolytic and sympatholytic activities have been attributed to the drug, but these offer by no means adequate explanation of its mechanism of action.

Clinical Observations.—

Investigations on the hemodynamic properties of Apresoline in human subjects have been carried out by Schroeder,[22, 23] Page,[24] Freis,[25, 26] Hafkenschiel,[27] and others.

Schroeder has treated patients with essential and "renal" hypertension with Apresoline orally or intramuscularly. He observed significant reduction in the blood pressure and amelioration in the subjective symptoms. The drug

*Apresoline was generously furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

was very effective in malignant hypertension and in patients who have had unsuccessful sympathectomy as treatment for their hypertension. In 14 out of 15 patients treated by Schroeder, albuminuria diminished or disappeared some time during the treatment. This author believes that this drug is of real value in the management of hypertensive states, since through its vasodilator effect some of the damage to the cardiovascular system can be prevented.[23]

Freis and his co-workers gave the drug intravenously and orally to normotensive and hypertensive subjects. They obtained a fall of 8 to 16 per cent in the diastolic blood pressure, after a latent period of 8 to 10 minutes. Some of their patients treated orally did not show any blood pressure fall. The same authors found modification in the vasopressor reflexes (cold pressor and Valsalva "overshoot") produced by Apresoline. This led them to believe that the drug has some sympatholitic activity.

Page studied 70 patients with essential hypertension; in 33 he obtained a fall of 20 mm. Hg in the diastolic pressure, while in the remaining patients variable results were observed.

Hafkenschiel and Lindauer observed significant reduction in the diastolic pressure with oral Apresoline in certain cases of essential hypertension, while in others the result was negligible. The same group showed that the drug releases the cerebral vascular resistance.

The effect of the drug on renal hemodynamics in human subjects was first studied by Reubi[28, 29] and later by Schroeder, Page, and in our laboratory.[30] These authors believe that a significant increase in renal blood flow is usually observed during the hypotensive period concomitantly with a decrease in filtration rate. The filtration fraction is diminished. The urine volume shows inconsistent changes.

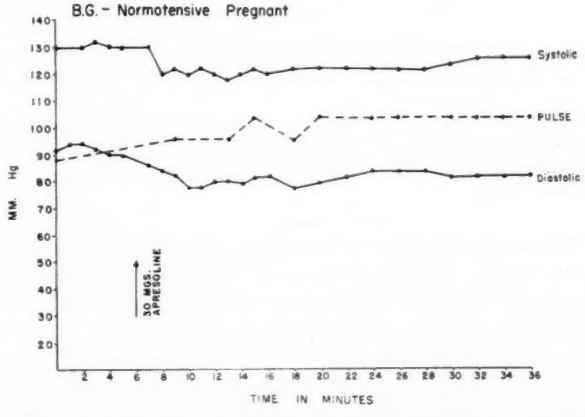

Fig. 1.—The effect of 30 mg. of Apresoline intravenously on the blood pressure of a normotensive pregnant subject. Note the slight drop in the diastolic blood pressure and the tachycardia.

Hypertensive Complications of Pregnancy.—

In this department, Apresoline was given intravenously to 47 patients; among these there were 17 with acute toxemia of pregnancy (1 eclamptic patient) and 13 with essential hypertension associated with pregnancy. The remaining were normotensive subjects. In addition, 10 with acute toxemia (1 eclamptic patient) and 2 with essential hypertension associated with pregnancy were treated by Kistner and Hellman at the Kings County Hospital with the same technique utilized here. The results show slight changes in the blood pressure of the normotensive group after intravenous doses varying from 10 to 50 mg. (average 30 mg.) (Figs. 1 and 3). On the other hand, the effect of

the same dosage on the hypertension of acute toxemia is strikingly different. Ten to 12 minutes after the intravenous administration of a single dose the blood pressure begins to fall, the diastolic prior to and more markedly than the systolic; and 30 minutes after the injection, blood pressure levels become normal and remain so for periods varying from 4 to 22 hours. The average blood pressure fall in the toxemic group was 26 per cent systolic and 43 per cent diastolic (Figs. 2 and 3). During the hypotensive phase, the subjective symptoms of toxemia are usually improved and patients experience peculiar side effects which will be described later.

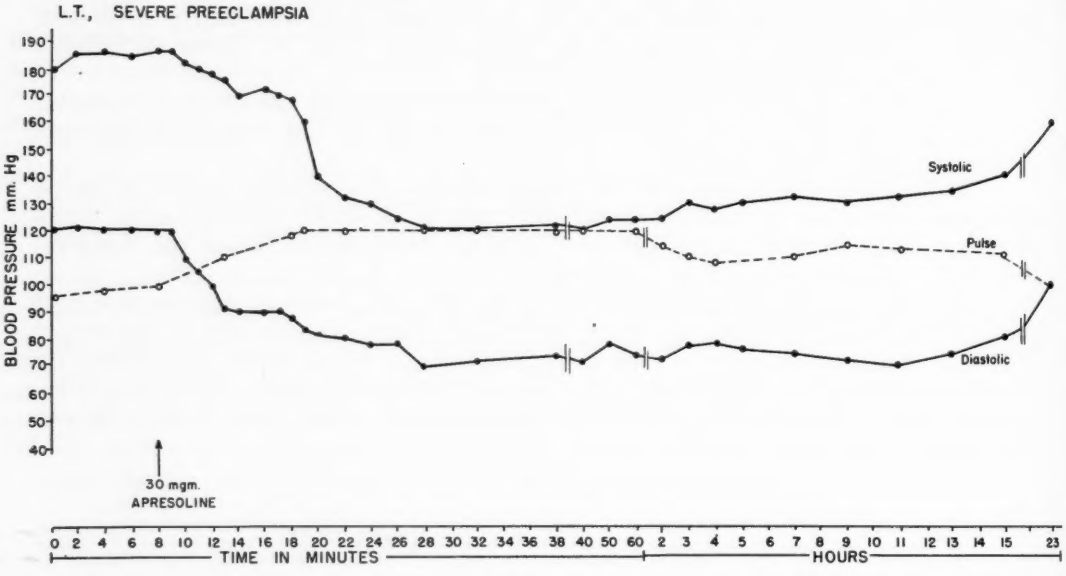

Fig. 2.—The effect of 30 mg. of Apresoline in severe pre-eclampsia. This patient had hypertension, edema, and proteinuria. She was somewhat disoriented but had no convulsions. Note the marked drop in both systolic and diastolic blood pressure. The hypotensive effect lasted for approximately 23 hours. The patient's general condition improved one hour after the administration of the drug.

The effect of the same intravenous dose on essential hypertension associated with pregnancy is not as striking as in toxemia; an average of 11 per cent systolic and 19 per cent diastolic fall was observed (Fig. 4). Detailed data on these observations will be published elsewhere.[31]

Further studies were carried out in our laboratories in normal as well as toxemic subjects on the effects of this drug on the renal hemodynamics, excretion of electrolytes, cardiac output, skin temperature, and vasopressor reflexes (Figs. 5 and 6). For the kidney studies, the technique of osmotic diuresis with mannitol in hydropenia was employed, for in pregnancy this technique offers a series of advantages which cannot be had with the conventional methods.[32] The results indicate that Apresoline increases the blood flow to the kidneys in most cases. The glomerular filtration rate and filtration fraction are, however, decreased. The urine volume remains constant or is slightly diminished. The urinary concentration of sodium and chloride is either diminished or unchanged, while that of potassium usually rises. These changes in renal hemodynamics are of temporary duration and a return to normal is observed even though the blood pressure remains at low levels.

One notable feature of this drug in toxemia is its effect on renal vascular resistance and cardiac output. The resistances of both afferent and efferent arterioles as calculated by Gomez'[33] formulas are reduced, the latter somewhat

more than the former. This explains to a certain extent the reduction in filtration rate and filtration fraction since these two functions depend on the dynamic differences between afferent and efferent arterioles. Cardiac output and cardiac forces as determined by the ballistocardiograph are usually increased following Apresoline. The skin temperature of the upper extremities is more markedly increased than that of the lower extremities, a finding which as yet has no explanation and is at variance with what is seen with the ganglionic blocking agents. Most of the vasopressor reflexes such as the pressor reaction to cold and Valsalva "overshoot" are not totally abolished, indicating that the drug does not seem to block the autonomic nervous system. Complete data on these findings will be the subject of another report.[34]

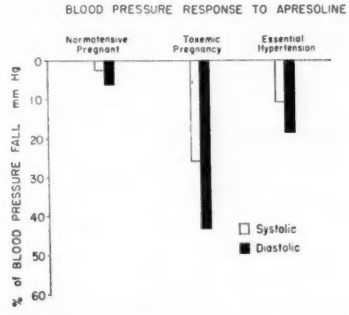

Fig. 3.—Mean blood pressure response to Apresoline in 47 cases. Note the difference between the group with toxemia of pregnancy and essential hypertension. The diastolic fall is always more marked than the systolic.

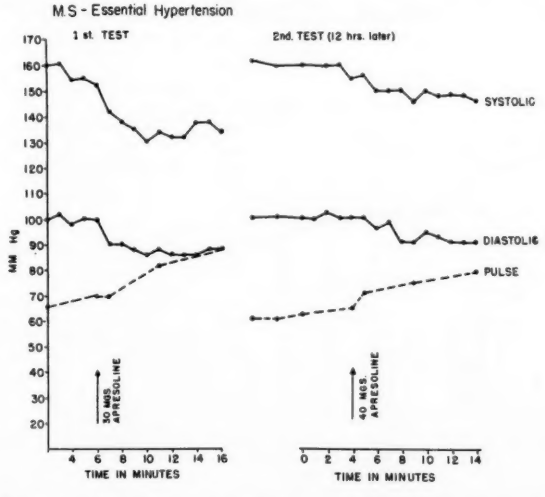

Fig. 4.—The effect of 30 and 40 mg. doses of Apresoline in essential hypertension associated with pregnancy. The fall is not as marked as in toxemia. Tachycardia is invariably present. In the second test, some tolerance to the drug is noted.

Side Effects.—

Tachycardia is invariably present but is not related to the magnitude of blood pressure fall. Feeling of warmth all over the body, particularly in the upper extremities, is present. Sensation of fullness and throbbing of the head and headache are very frequent but seldom are of such a magnitude as to warrant interruption of the treatment. Sensation of epigastric fullness and aching is experienced occasionally. Some authors report occasional nausea

and vomiting but in our series these side effects were not observed. Most of these manifestations are attributed to the vasodilatation induced by the drug, and rarely require any specific treatment. It is notable that the patients with acute toxemia tolerated the drug better than those with essential hypertension, although in the former group the vasodepression was more marked.

Oral and Intramuscular Routes.—

In this department Apresoline was also given orally to pregnant subjects with essential hypertension and toxemia in doses varying from 200 to 400 mg. daily. No consistent changes in the blood pressure were observed, although with the larger doses some of the side effects became evident. The intramuscular administration of the drug also failed to produce any significant reduction in the blood pressure. The discrepancy between our results and those reported by others regarding the efficiency of the oral route might be due either to the smaller dosage employed by us or to some other reasons which cannot be explained at present.

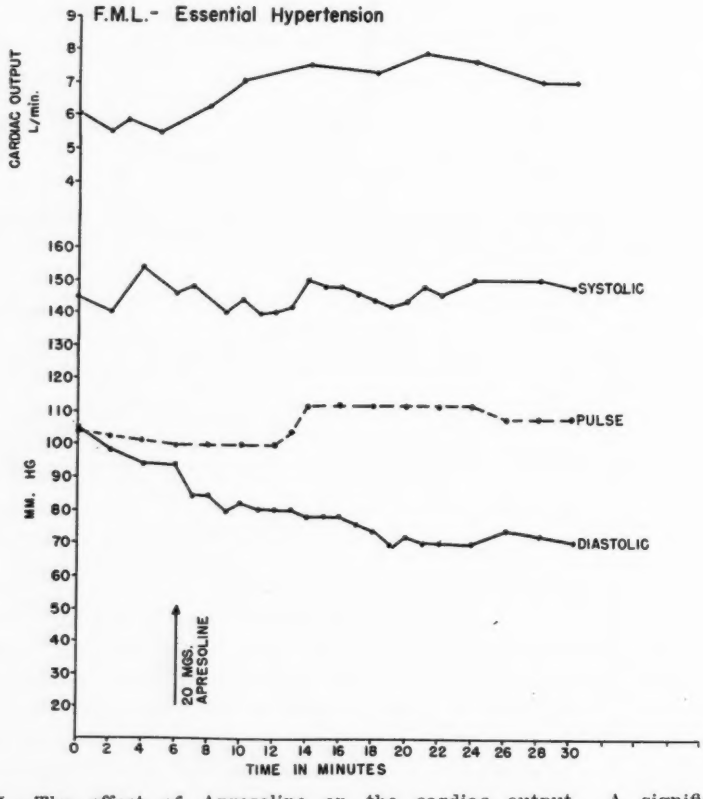

Fig. 5.—The effect of Apresoline on the cardiac output. A significant increase in cardiac output is observed at the height of fall in blood pressure. This increase is due to a rise in the stroke volume and pulse rate.

Thiophanium Compounds

Randall, Peterson, and Lehmann[35] were the first to find out that certain pharmacologic activities of some thiophanium derivatives were similar in many respects to those of tetraethylammonium ion (TEA). In certain animals, the ganglionic blocking and vasodepressor action of these compounds was 30 times more potent than that of TEA. Furthermore, in animals, some of these com-

pounds were active by both the intramuscular and intravenous routes, although by the former about 20 times the effective intravenous dose was required to produce the same vasodepression.[35] One of these compounds, which commercially has been called Arfonad,* has been more intensively studied. This drug blocks the autonomic nervous impulses at the ganglionic level, thus producing a hypotensive effect which is more marked when the blood pressure is supported by increased neurogenic tone. This vasodepression can be practically abolished by epinephrine, norepinephrine or ephedrine.[35]

In human subjects, a few studies on the hemodynamic properties of Arfonad have been carried out by Sarnoff and associates,[36] Green,[37] McCubbin and Page,[38] and Assali and Douglass.[39]

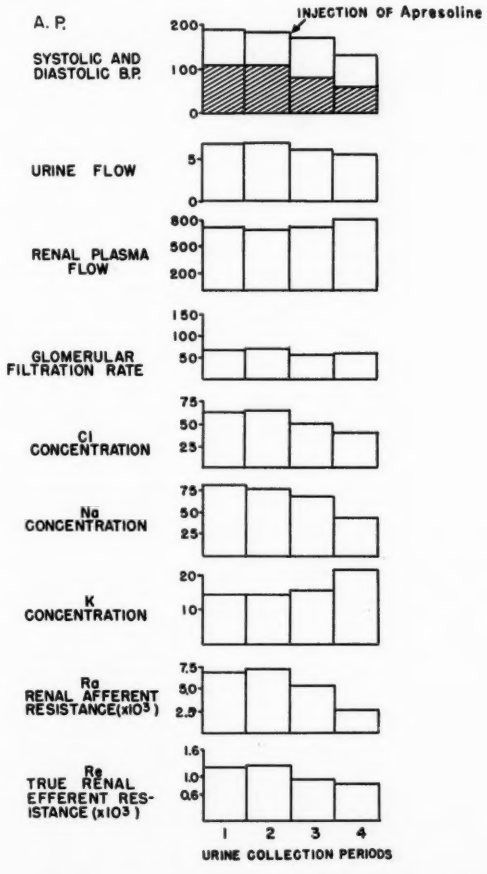

Fig. 6.—Renal hemodynamics and the excretion of electrolytes are illustrated. The technique of osmotic diuresis with hypertonic mannitol in hydropenia was employed. Note the rise in renal plasma flow and the decrease in both afferent and efferent renal resistances after the injection of the drug.

Sarnoff and co-workers[36] have given the drug to subjects with essential hypertension by single intermittent intravenous injections and by intravenous drip infusion with 5 per cent glucose and water. While with the former method a brief but marked fall in blood pressure is observed, with the latter

*Arfonad was generously supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

the same fall can be prolonged for as long as the intravenous drip is allowed to run. These authors believe that the drug also reduces the pulmonary capillary pressure, thereby preventing or improving pulmonary edema. Green observed a fall in the blood pressure and rise in the skin temperature of the lower extremities after intravenous doses of Arfonad.

In this department a study has been carried out during the past year with Arfonad using the single intravenous injections and the intravenous drip infusion methods. A total of 54 patients has been tested. Among these, there were 16 with essential hypertension associated with pregnancy and 10 with acute toxemia of pregnancy. The remaining were normotensive nonpregnant and pregnant subjects.

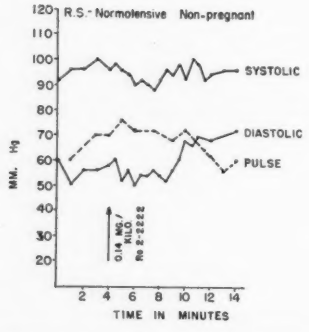

Fig. 7.—The effect of 0.14 mg. per kilogram of Arfonad on a normotensive nonpregnant subject. No appreciable change in blood pressure is seen.

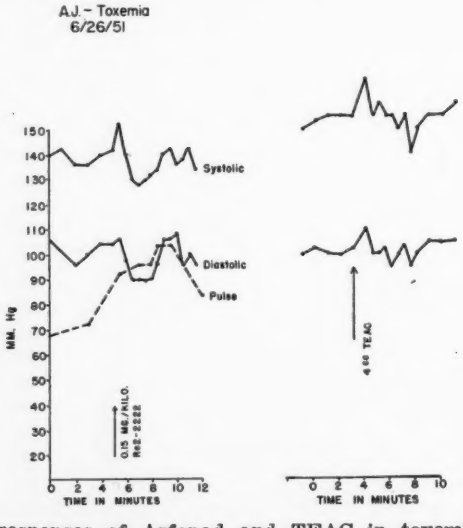

Fig. 8.—Comparative responses of Arfonad and TEAC in toxemia of pregnancy. No blood pressure changes are seen with either drug.

Our results indicate that Arfonad given by single intravenous doses of 0.1 to 0.2 mg. per kilogram evokes in the normotensive pregnant and essential hypertensive groups a marked drop in the blood pressure lasting from 3 to 10 minutes. The effect of the same dosage on normotensive nonpregnant and toxemic subjects is negligible (Figs. 7, 8, 9).

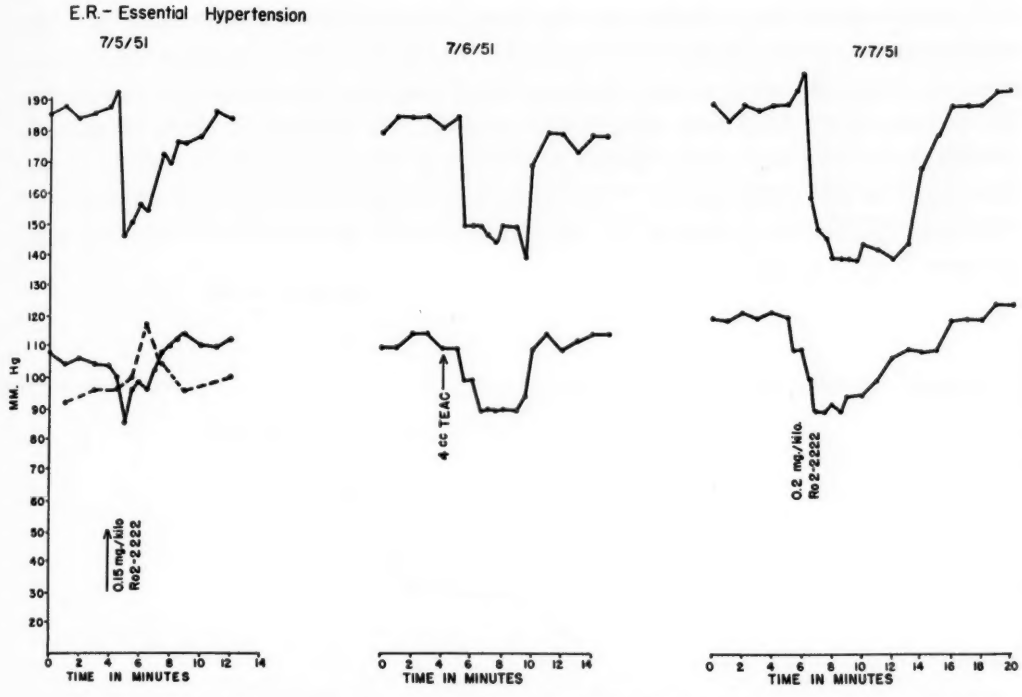

Fig. 9.—Comparative results obtained with different doses of Arfonad and a standard TEAC test in essential hypertension associated with pregnancy. The effect of both agents was practically parallel.

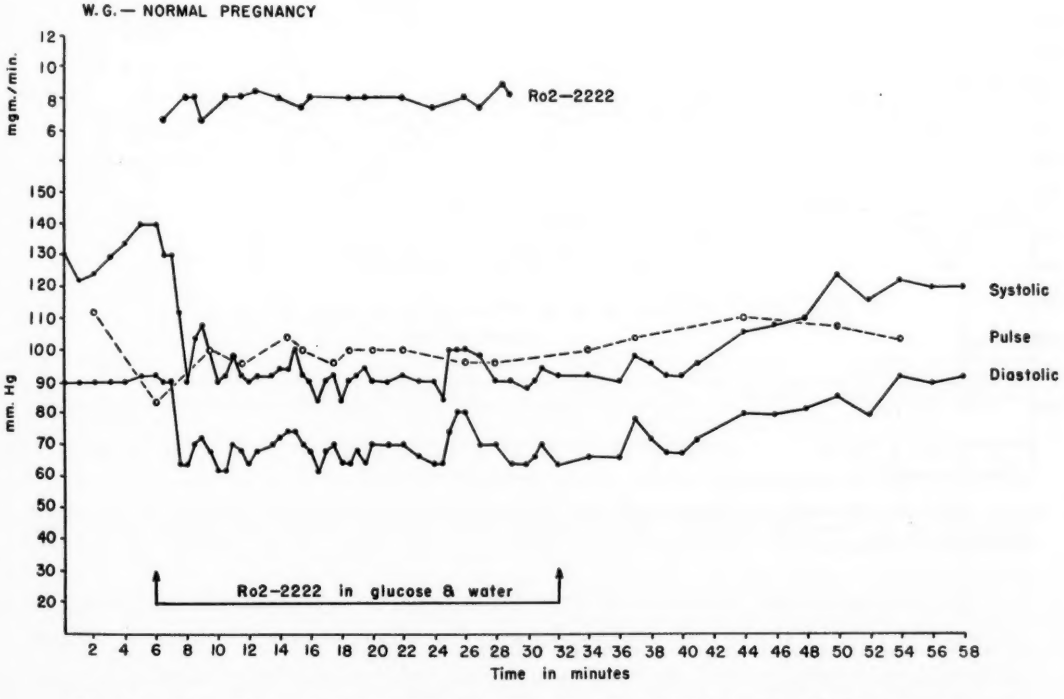

Fig. 10.—The effect of intravenous drip infusion of Arfonad on the blood pressure of a normotensive pregnant subject. Note the marked drop which remained for some time after the interruption of the infusion. This denotes certain cumulative effect of the drug.

Intravenous drip infusion of the drug in amounts varying from 4 to 36 mg. per minute also produces a marked drop in the blood pressure of normotensive pregnant subjects and subjects with essential hypertension, averaging 35/46 mm. Hg. This fall lasts for as long as the infusion is allowed to run, although in some instances cumulative effect is observed, while in others some tolerance to the drug occurs. The drip method is also much less effective in reducing the blood pressure of the toxemic and normotensive nonpregnant groups (Figs. 10, 11).

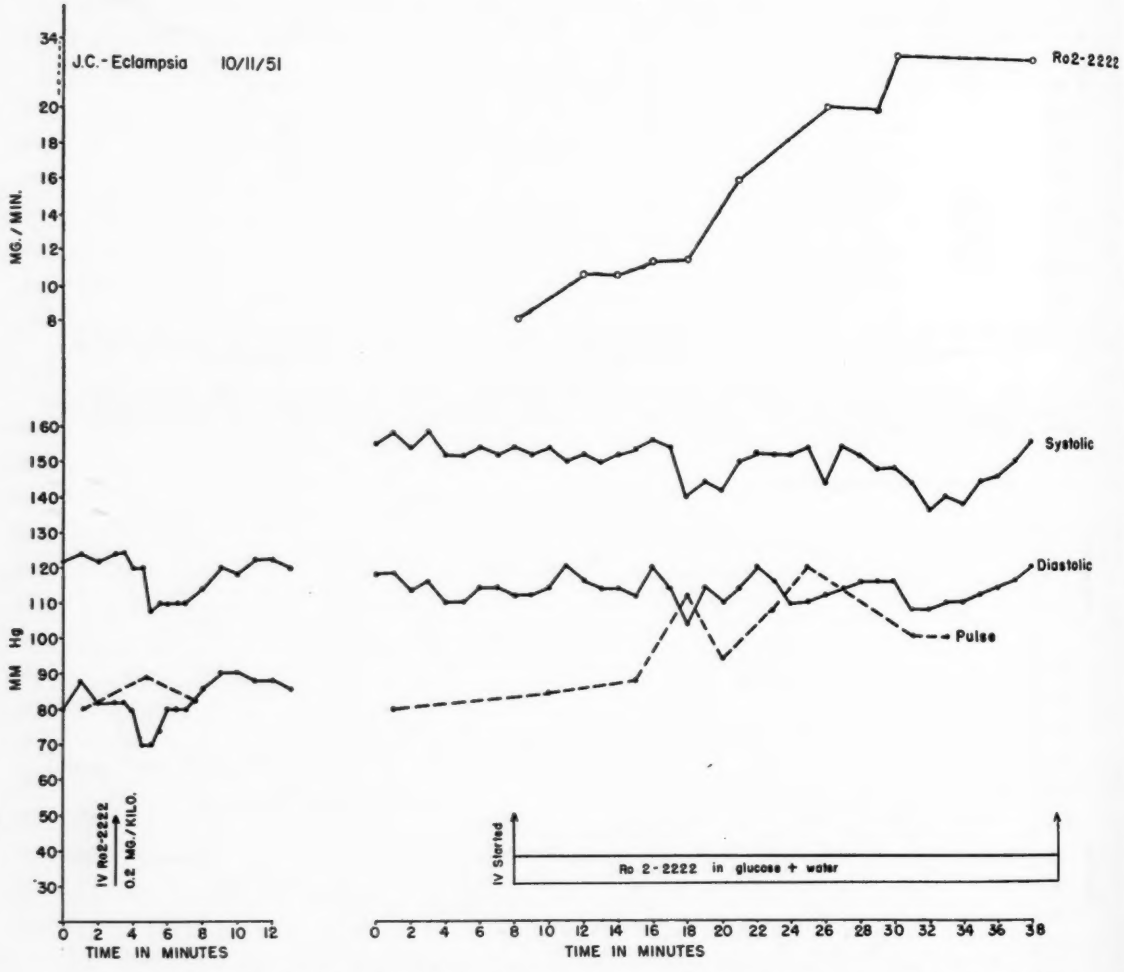

Fig. 11.—The effect of acute injection and intravenous infusion of Arfonad on the blood pressure of an eclamptic patient. Note the negligible response despite the higher rate of the intravenous drip.

In the use of the intravenous drip technique, it is frequently necessary to adjust the rate of the infusion according to the blood pressure response. Thus, frequent readings have to be taken and close individual observation of the patient's reaction is mandatory. In our hands, there seems to be no correlation between the effective dose and the patient's weight; hence, the effective dose has to be adjusted for each case.

In some of our cases Arfonad was given by intramuscular injections. This route, however, was of no value in reducing the blood pressure of any patient.

Other hemodynamic properties of Arfonad were investigated in this department.[34, 39] It was found that at the height of vasodepression postural hypotension is usually present, the cold pressor test is partially or totally blocked, and the cardiac output is diminished in most cases. Renal blood flow, glomerular filtration rate, and urine flow as determined by the osmotic diuresis

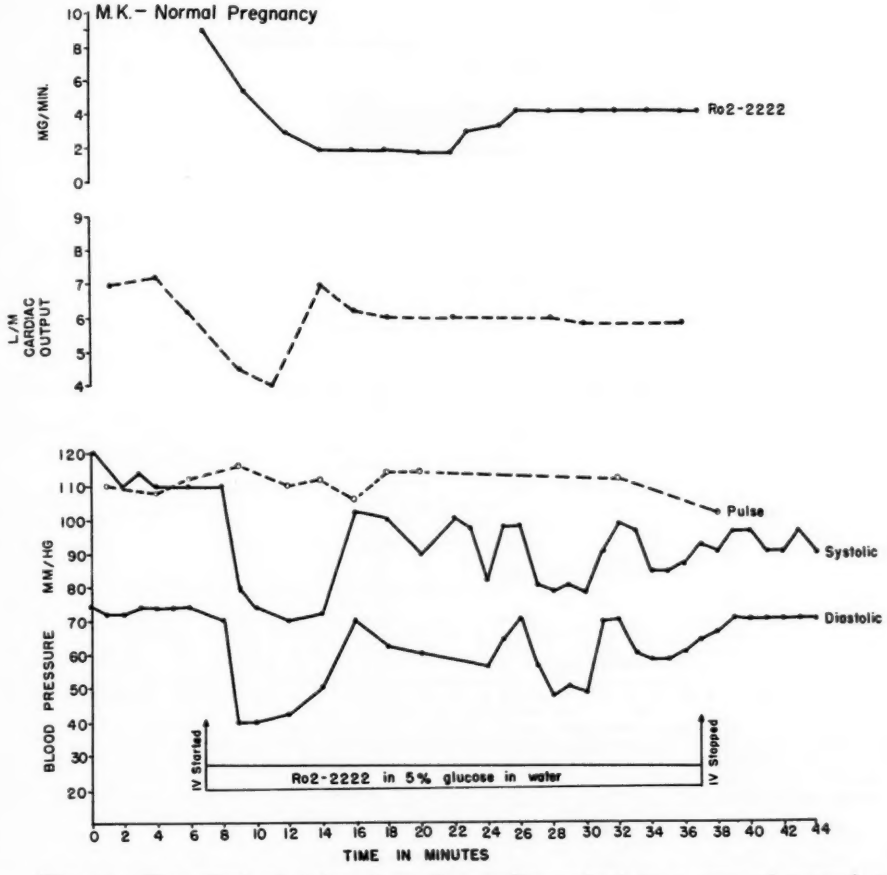

Fig. 12.—The effect of Arfonad on the cardiac output in a case of normal pregnancy. The drop in blood pressure was accompanied by a marked drop in the cardiac output which was due mainly to a drop in the stroke volume. A return to normal is observed shortly thereafter.

technique are usually reduced. The over-all renal resistance is markedly increased (Figs. 12 and 13). The skin temperature of the lower extremities rises more markedly than that of the upper extremities. These hemodynamic changes caused by Arfonad in pregnancy resemble closely those observed with other autonomic blocking agents, particularly high selective spinal anesthesia and contrast entirely with what is observed with the phthalazine compounds.[6, 7, 32] However, as in the case of the latter drugs, the effects of Arfonad on kidney functions are of short duration and a rapid restoration to normal is achieved. All the data on Arfonad experiments will be published elsewhere.

Side Effects.—

The side effects produced by Arfonad are similar to those observed with other autonomic blocking agents.[6, 7] Tachycardia which is more marked with single injections than with intravenous drip is observed in most cases. Nausea, vomiting, tingling, and sensation of warmth of the lower extremities frequently occur. Symptoms of shock may appear in a few cases in which a sudden and severe drop in blood pressure is seen. These symptoms can be corrected immediately by elevating the legs 90 degrees or by the injection of epinephrine or epinephrine-like substances.

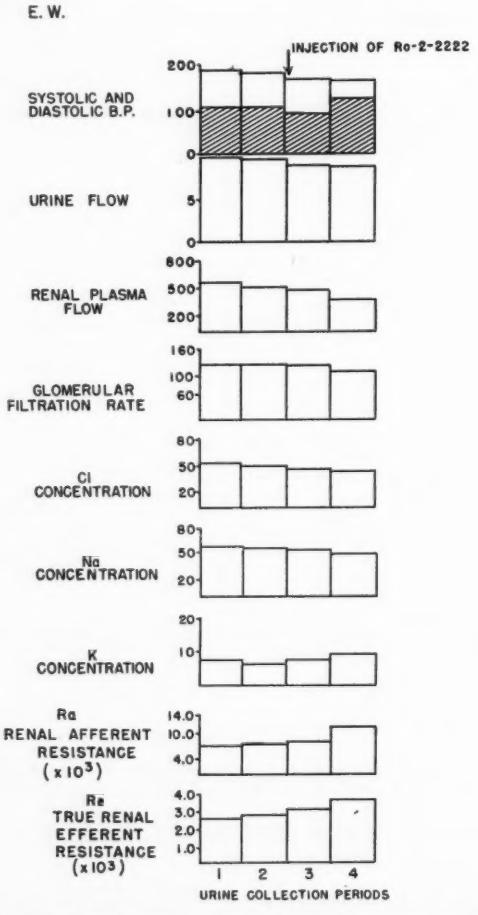

Fig. 13.—The effect of Arfonad on the renal hemodynamics and the excretion of electrolytes. Note the fall in renal plasma flow and the rise in renal resistances after the administration of the drug.

Combination Therapy.—

A series of drug combinations has been suggested and put on trial in prolonged treatment of essential hypertension. Apresoline and hexamethonium compounds were used by Freis and his co-workers[40] and others[23] with some success.

In this department a preliminary experiment with a combination of Apresoline and veratrum derivatives has been attempted in the treatment of toxemia of pregnancy. Patients were given half of the effective dose of each compound in a single intravenous injection. The fall in blood pressure was equal to or more than that obtained with either drug when given in full dosage

separately (Fig. 14). The tachycardia produced by Apresoline and the bradycardia of veratrum cancelled each other and the pulse rate remained practically unchanged. The other side effects of both Apresoline and veratrum were absent since the doses of each drug given were too small to produce any appreciable manifestation. Thus, the combination of Apresoline and veratrum seems to offer a promising method for the treatment of toxemia of pregnancy. Further studies on the potentiating effects of these two agents both in man and animal are in progress.

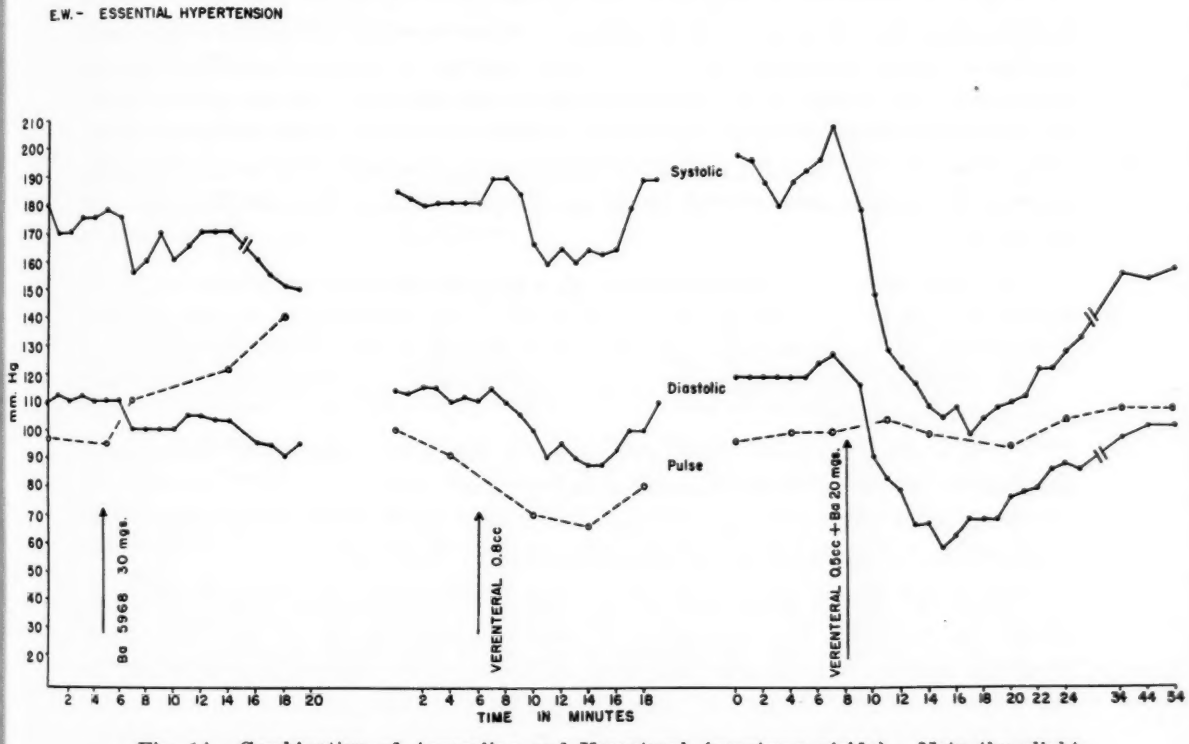

Fig. 14.—Combination of Apresoline and Verenteral (veratrum viride). Note the slight change in blood pressure after 30 mg. of Apresoline and 0.8 c.c. of Verenteral given separately. Note also the tachycardia after Apresoline and bradycardia after Verenteral. When the two drugs were given together in smaller dosage, the fall in blood pressure was more marked and the pulse rate remained at control rates.

Comment

Adequate explanation of the cause of most of the hypertensive complications of pregnancy is as yet not available. This is particularly true in the case of the specific syndome called acute toxemia of pregnancy. In view of this lack of knowledge regarding the etiology of the disease, one has to resort empirically to the treatment of the predominant pathophysiological process involved which, in our concept, is arteriolar vasoconstriction and hypertension. That this pathologic process is underlying most forms of hypertensive diseases and is doing some damage to the cardiovascular system of the patient is attested to by numerous publications.[2, 23, 40-43] The question of whether or not arteriolar vasoconstriction and hypertension are primary or secondary becomes merely of academic interest. Thus, any agent which could produce ar-

teriolar dilatation and lowering of the blood pressure without decreasing, for appreciable time, the cardiac output and blood flow to the major organs is of some value in hypertension.

From the practical viewpoint, successful treatment of a pregnant patient with hypertensive complication depends on accurate differential diagnosis between the three most common clinical entities: (a) acute toxemia, (b) essential hypertension, and (c) acute toxemia superimposed on essential hypertension.

Since it has been shown that the hypertension of acute toxemia of pregnancy responds very poorly to autonomic and adrenergic blocking agents such as TEAC, spinal anesthesia, etc.,[2, 5, 6, 8] it is logical to assume that these agents have very little place in the management of this disease. On the other hand, the hydrazinophthalazine or veratrum derivatives or the combination of both seem to be by far the most suitable agents for the treatment of acute toxemia. Among the advantages offered by Apresoline alone or in combination are the following:

A. Simplicity of administration: A single intravenous injection of 30 to 40 mg. brings about a progressive fall in the blood pressure to normal levels; a repetition of the injection may not be needed for a long period of time.

B. The side effects are minimal and can be easily tolerated by any patient with acute toxemia.

C. The drug releases renal and cerebral vascular resistances which have been shown to be markedly increased in toxemia.[44, 45]

D. It also increases the cardiac output and renal blood flow, thereby reversing some of the pathophysiological processes involved.

When the case is diagnosed as essential hypertension associated with pregnancy, theoretically the treatment of choice would be one of the autonomic blocking agents, because the majority of these cases respond much better to this type of drugs. However, since very few of these patients require emergency treatment which usually results in acute drop in the blood pressure, their management assumes a different aspect. Long-acting drugs preferably if active by the oral route are most advantageous for these cases. As far as we know at the present, none of these drugs fulfill these requirements, because either they are ineffective or the side effects and tolerance are so severe that their prolonged use becomes impractical.

When a case of essential hypertension assumes a malignant form with or without encephalopathy—an event which is rarely seen by obstetricians—or when an acute crisis of pulmonary edema becomes imminent, the use of the autonomic blocking agents should be seriously considered.

Tetraethylammonium chloride is a short-acting drug and its use by intravenous infusion has been unsuccessful. Spinal anesthesia can be employed but it needs specialized skill and training. On the other hand, Arfonad given by intravenous drip infusion seems to give successful results in reducing acutely the blood pressure of most of these patients for a fairly long period of time. The administration of this drug, however, should receive careful attention, particularly in regard to frequent blood pressure readings and readjustment

of the rate of infusion. The fact that Arfonad, like any other autonomic blocking agent, decreases the cardiac output and renal blood flow and increases the renal resistance should not warrant the preclusion of its use when indicated. These hemodynamic effects are probably caused by pooling of blood in the venous side of the circulation due to blockade of the venomotor tone. They are temporary and harmless to the patient.

The combination of acute toxemia with essential hypertension can be treated successfully with either phthalazine and/or veratrum or with thiophanium compounds. In our hands, the combination of these two illnesses has responded equally well to either drug. However, since Apresoline and/or veratrum are much easier to handle and administer, and because of their action on the cardiac output, renal vascular resistance, and renal blood flow, they should be attempted first. In case these drugs fail to produce adequate vasodepressor effect, Arfonad can then be given by intravenous drip infusion with the precautions already discussed.

Summary and Conclusions

Two new groups of synthetic vasodepressor drugs, the phthalazine and thiophanium derivatives, have been added to the clinical armamentarium for the treatment of hypertensive diseases with or without pregnancy.

The phthalazine compounds act through an as yet unknown mechanism. They are effective against a variety of hypertensive conditions, but they seem to be more specific against hypertension of acute toxemia of pregnancy. Even when given by intravenous injections, their action lasts for a long time.

The thiophanium compounds are ganglionic blocking drugs and their effect is more pronounced in the neurogenic type of hypertension. Their action is of short duration but it can be prolonged by intravenous infusion.

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INTRAVASCULAR CLOTTING COMPLICATIONS OF PREGNANCY*

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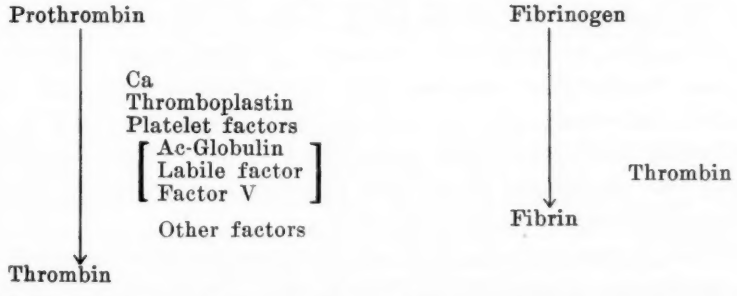
ABNORMALITIES in blood coagulation remain the major source of maternal mortality, despite the great advances in both obstetrical care and transfusion therapy. With the newer knowledge of blood coagulation, it now appears possible that we may be able to attack some of the heretofore obscure problems and to some extent throw light upon the etiology of certain of these blood-clotting abnormalities of pregnancy.

The Biochemistry of Blood Clotting

Our comprehension of the blood-clotting process is in rapid flux. Current concepts have been well summarized in recent reviews (Astrup,[1] Quick,[2] Stefanini,[3] Seegers[4]). Although a difference of opinion exists concerning the meaning of the new findings, there is general agreement about the central elements of the process. For our purposes, these may be summarized as follows:



Thrombin is formed from prothrombin, the transformation being mediated, in some unknown way, by calcium, thromboplastin, platelet materials, Ac-globulin, and possibly other factors not yet disclosed. In the second phase of the reaction, fibrinogen is enzymatically converted to fibrin by thrombin. This limited, static account omits the earlier stages of the reaction, involving the possible elaboration of active components from precursors, the whole anticoagulant complex, and does not show the cyclic nature of some of the intermediate reactions which speed up the process. However, it suffices to state, in brief, that in circulating fluid blood there is an equilibrium between the clot activators and accelerators on the one hand, and the clot inhibitors and destroyers on the other. The delicate balance maintained by this dynamic process provides for the normal fluidity of the blood, its rapid transformation to a clot at the site of endothelial damage, the prevention of the extension of

*Presented at a meeting of the Philadelphia Obstetrical Society, Jan. 3, 1952.

the clot, and the subsequent dissolution or organization of the clot. The formation of the clot is an autocatalytic, chain-reaction process. That is, the reaction, once started, not only propagates itself, but accelerates to a sudden end point. It should be emphasized that the end point of the process is the formation of fibrin which, laid down in a mesh at the site of endothelial injury, forms the matrix of the red thrombus around the white thrombus cluster of platelets. It is this whole complex which forms the familiar blood clot. However, fibrin alone can be formed and disseminated in the circulating blood as "fibrin emboli"[5] and in such an instance can be deposited in the vessels in vivo. The completed process may result in either generalized coagulation and thrombosis or in the very opposite, defibrination and incoagulable blood, depending, in a large part, upon the quantity of the coagulating factor. A large dose of thromboplastin, or thrombin, may cause massive clotting and death; smaller doses may render the blood incoagulable.[6]

Blood Coagulation in Pregnancy

These observations, derived mainly from experimental studies on animals,[7] have lately been brought to bear on clinical problems with beneficial effects. Certain disorders of late pregnancy, especially those accompanied by premature separation of the placenta, are frequently attended by severe bleeding. It has been amply demonstrated that this hemorrhagic diathesis is in some instances due to a defect in the coagulation mechanism, particularly fibrinopenia (Dieckman, 1936,[8] Reid, 1950[9]). Page[10] and Schneider[5, 7, 11, 12] have shown further that the fibrinopenia in many cases is the result of defibrination. Schneider, in particular, through a critical analysis of the literature and by means of controlled experiments on animals, correlated with careful clinical studies, has been able to establish the salient features of the blood-clotting dyscrasia associated with some cases of premature separation of the placenta and has assembled them into a syndrome which he calls "thromboplastin complications of pregnancy."[11]

The relation between premature placental separation, intravascular clotting, and subsequent incoagulability of the blood rests primarily on the role of thromboplastin as a trigger substance, one initiating the clotting process. In the course of the premature separation of the placenta, the thromboplastin-rich fragments and extracts of placenta and decidua mix with the blood of the retroplacental hematoma and enter, thence, by several possible pathways the maternal circulation. The entrance of the thromboplastin into the general circulation upsets the delicate balance between pro- and anticoagulants maintaining fluidity and initiates the clotting process. A large quantity of thromboplastin may result in massive clotting and pose the dangers of thrombosis and thromboembolism. A smaller quantity, maintained over a period of time, will result in defibrination of the blood and subsequent incoagulability, giving rise to the threat of hemorrhage. Both stages have been observed in the same patient as well as in separate patients. There seems little doubt that this construct actually reflects the etiology of some of the disorders of late pregnancy associated with premature separation of the placenta, and

provides the basis for a rationale for the treatment of these disorders. Whether these concepts will also be able to provide a satisfactory etiological factor for some of the toxemias of pregnancy remains to be seen.

Case Reports

Our interest in this pathologic process was aroused by a patient with abruptio placentae who also presented a failure of the clotting mechanism (Case 1). An unawareness of this entity permitted us to make the working diagnosis soon after the initiation of the pathologic process in our second patient, one who exhibited an extreme abnormality in intravascular clotting (Case 2). Our experience with the second case extends our knowledge of this pathologic process and, as a consequence, we should like to present the thesis that, in certain circumstances, it may be necessary to go beyond the simple interruption of pregnancy, as Schneider recommends[11, 13] and resort to hysterectomy to save the life of the patient.

CASE 1.—M. S., a 46-year-old Negro gravida x, para ix, a prenatal clinic patient, entered the hospital at term in early labor, April 19, 1950. Admission examination revealed pregnancy at term, blood pressure 140/95, plus one to two pitting pretibial edema, large-sized fetus with the head fixed in the pelvic inlet but not engaged and good fetal heart sounds in the left lower quadrant. The membranes were intact, the cervix dilated to one finger with but 50 per cent effacement. There was no vaginal bleeding. Pains were occurring every 4 to 5 minutes, 30 seconds in duration, but of poor quality. About five hours after admission the patient suddenly developed continuous abdominal pain. The uterus became tender and seemed to increase in size. Fetal heart sounds could no longer be heard. There was no external bleeding. A diagnosis of placentae abruptio with concealed bleeding was made. Intravenous fluids were started, the membranes ruptured, and the almost completely dilated cervix pushed out of the way. A 10 pound, 13 ounce, stillborn male infant was delivered easily with outlet forceps. The placenta was delivered immediately, followed first by huge clots and then by massive free uterine bleeding. Uterine packing, uterine massage, and oxytocics were futile. Accordingly, a rapid subtotal hysterectomy was performed. It was noted that there was a great deal of oozing from all areas. There was no evidence of rupture of the uterus and examination following hysterectomy revealed an intact cervix and vagina. The patient was maintained in good condition by the constant use of whole blood, some of it delivered rapidly under pressure.

Three hours after operation the patient went into shock, while still receiving a transfusion. Examination pointed obviously to intra-abdominal hemorrhage. The patient was immediately operated upon and the abdomen was found to contain approximately 1,200 c.c. of blood. Again, it was evident that the bleeding was coming not from any free bleeding vessels, but from many points over the cervical stump and parametrial areas. Some of these oozing points were ligated with suture ligatures, the pelvic cavity was packed and the abdomen closed with through-and-through sutures. During the delivery and operative procedures, she received thirteen 500 c.c. transfusions of whole blood (6,500 c.c.).

Pathologic Examination.—

Macroscopic: The specimen consisted of a markedly enlarged, supravaginally amputated uterus measuring 18 by 15 by 12 cm. The serosal surface was smooth, grayish pink, and markedly hemorrhagic at the cornua. The myometrium was thickened, averaging 4.5 cm. in the fundus. It was firm, grayish red, and had a beefy appearance. The endometrial canal was markedly distended. It was lined by a shaggy hemorrhagic tissue which, in the left cornu, had a membranous and bullous appearance. The bullae were filled with blood. No hemorrhage into the wall was demonstrated except at the right cornu where there was subserosal hemorrhage.

Microscopic: Sections of the uterus revealed a markedly hypertrophied wall. The endometrial lining was replaced by decidual and trophoblastic tissue. No chorionic villi were seen. Focal subserosal hemorrhage was noted.

CASE 2.—C. D., a 24-year-old white woman, had her first pregnancy in 1948. During this pregnancy she developed severe pre-eclampsia and was delivered, vaginally, of a stillborn infant in the eighth month. Her postpartum course was marred by thrombophlebitis of both legs which responded well to medical treatment.

One year later, after being studied thoroughly medically by means of kidney function tests, eye-ground examination and electrocardiograms, she was permitted to become pregnant again. This time she bled early in the third month, and evacuation of the uterus was necessary because of incomplete abortion. This postoperative period was again complicated by a thrombophlebitis of both legs. It, as before, responded to medical treatment. After once again being studied and found normal, the patient was allowed to become pregnant in August, 1950. She was placed on the Smith and Smith stilbestrol regime because of her previous toxemia and miscarriage. Her pregnancy progressed normally except for a constant hypotension (80-90/60-40). At the beginning of the sixth month the patient suddenly developed evidences of cerebral thromboses with an associated right-sided hemiplegia and with some abnormal neurologic signs on the left side of the body.

Although the etiology of this "accident" was obscure, we were immediately alerted to the possibility that this might represent an instance of an intravascular blood-clotting complication of pregnancy. The laboratory findings in this connection are summarized below.

The prothrombin time (modified Quick one-stage) the recalcified clotting time in glass and silicone, the bleeding time, the protamine titration[14] and the antithrombin titer[15] were essentially normal. The Lee-White clotting time was, possibly, slightly accelerated.

A series of tests, investigating the possible clot-accelerating effect of the patient's plasma, were performed in the period January 27 to February 1. Patient's deprothrombinized plasma, critically adsorbed with $Ca_3(PO_4)_2$,[16] was mixed in several proportions with whole plasma and one-stage prothrombin times determined. The study showed that the patient's plasma had a marked shortening effect on the prothrombin time of whole normal plasma on the first day. This effect gradually diminished until it disappeared on February 1. Although we cannot at this time evaluate the significance of these data, the trend was consistent and paralleled the clinical status of the patient.

The patient was treated with papaverine, nicotinic acid, and stellate ganglion block in an attempt to improve cerebral dilatation and blood flow. Plasma fibrinogen was obtained and kept on hand for use if fibrinogen depletion should occur. She was discharged from the hospital March 3, 1951, with some recovery of function of the right arm and with almost complete use of the right leg.

The pregnancy itself was apparently progressing normally. However, two weeks after discharge from the hospital, the patient developed an acute thrombosis of one of the vessels of the right leg without evidence of infection. She was immediately rehospitalized and received conservative treatment to which she appeared to respond.

On March 30, 1951, when she was seven months pregnant, she suddenly developed hypertension, albuminuria, and no longer felt fetal movements. Fetal heart sounds were not heard after April 1. Following this, her blood pressure returned to normal. The patient then showed signs of early labor. After due consideration and despite obvious fetal death, it was decided to do a cesarean section for the following reasons: (1) The neurosurgeon felt that the increased intracranial tension of labor should be avoided in the presence of an already damaged brain. (2) Active labor might exaggerate an already existing separation with severe bleeding on the basis of fibrinopenia and was therefore to be avoided. (3) Abdominal delivery would afford an opportunity to sterilize this patient and it was agreed that such a sterilization was indicated on the basis of her stormy obstetrical history. On April 3, therefore, a classical cesarean section and bilateral tubal ligation were performed. A macerated seven-month stillborn male fetus was removed. The placenta which measured 10 by 9 by 2.5 cm. demonstrated three old retroplacental clots. The largest occupied more than half the maternal surface and left a depression in that surface. The two other clots measured approximately 2 cm. in diameter and also depressed the maternal surface of the placenta. Histologically no significant findings were noted.

The postoperative course was surprisingly smooth and there were no obvious thrombotic or embolic episodes. She was discharged on the eleventh postoperative day.

Three days after discharge (the fourteenth postoperative day), the patient awakened from her sleep, complained of some vague abdominal cramps, became disoriented, and fell into a shocklike state. She was hospitalized within forty minutes but despite all measures died in less than one hour.

Pathologic Examination.—

The body was that of a young adult white woman, well developed and well nourished, and appearing the stated age of 24 years. The pupils were equal and were in middilatation. The pleural cavities were dry. A number of firm stringy adhesions were present at the left apex. The abdominal cavity contained 400 c.c. of dark serosanguineous fluid. The omentum was adherent to the anterior aspect of the uterus.

No evidence of aortic atherosclerosis was seen. The pulmonary artery, 4 cm. above the pulmonic valve on its anterior aspect, contained a wedge-shaped pink-tan, smooth-surfaced, adherent mass measuring 5 mm. in maximum diameter.

The inferior vena cava, at a level of 6 cm. above its bifurcation, contained a firm, friable, reddish-brown clot which was laminated by horizontal gray streaks. In areas this was adherent. The clot extended into the right common iliac vein and for a short distance into the internal and external iliac veins. The proximal end of this clot was smoothly rounded. Similar clotted material filled and distended the left renal vein. In the superior mesenteric vein, 2 cm. from its origin, there was extensive thrombus deposition which filled and distended the vein and many of its branches. The thrombus in the distal branches was irregularly scattered and separated by postmortem clots.

The heart weighed 200 grams. The valve cusps and leaflets had the usual configuration and were thin and delicate. On the auricular aspects of the mitral valve were pale pink friable vegetations. These had slightly beaded surfaces. The larger was present on the medial cusp and measured 8 by 4 by 2 mm.

The upper lobes of the lungs were pale pink and pinkish gray and from the cut surfaces there exuded moderate amounts of slightly bloody frothy fluid. In the lower lobes, and corresponding to areas of increased consistency, were red and reddish-purple, slightly friable, hemorrhagic areas, the pleural aspects of which projected slightly from the surrounding surface. These areas were present throughout all portions of the lower lobes. The major branches of the pulmonary artery and veins were free of thrombi. A number of the smaller arterial branches contained reddish-brown, firm, thrombotic masses.

The esophagus and stomach were essentially normal. The duodenum and jejunum were slightly distended and had a faintly cyanotic hue. The ileum, except for the terminal 20 cm., was slightly distended and had a superficially hemorrhagic appearance. The serosal surfaces were generally smooth. The proximal portion of the ileum was thin walled, with a slightly hemorrhagic mucosa and contained bloody material. Distally the wall was thickened to as much as 5 mm. The thickened wall was diffusely hemorrhagic with disappearance of the mucosal markings and with hemorrhagic material in the lumen. The distal ileum was faintly cyanotic but otherwise not remarkable. The demarcation between involved and normal ileum was fairly sharp. The entire colon was collapsed. Its lumen contained a small amount of bloody material. The mesentery of the small bowel was slightly thickened and edematous. Its venous channels were markedly engorged and contained multiple thrombi. The distal aspects of the mesentery were slightly thickened and edematous. Its venous channels were markedly engorged and contained multiple thrombi. The distal aspects of the mesentery were slightly hemorrhagic and markedly indurated. The mesenteric lymph nodes were diffusely and only slightly enlarged. Many were hemorrhagic.

In the upper pole of the right kidney and the lower pole of the left, vaguely defined pale yellow-tan wedge-shaped areas with prominent hemorrhagic streaks were present.

The uterus was slightly large, measuring 10 by 7 by 6 cm. The portal mucosa of the cervix was smooth. The os was elliptical. The canal was patent and contained a small

amount of mucus. The endometrial canal was patent, straight, and slightly distended. Just above the internal os the posterior aspect of the endometrial surface was covered by a small amount of green necrotic material. In the fundus the endometrial surface showed a raised, slightly polypoid, friable, reddish-tan, hemorrhagic area on the posterior and left lateral aspects. This measured 4 by 3 by 1 cm. The myometrium was of average thickness, measuring 2 cm. at the fundus. The posterior wall of the myometrium and the fundal portion contained numerous prominent vascular channels filled with clotted blood.

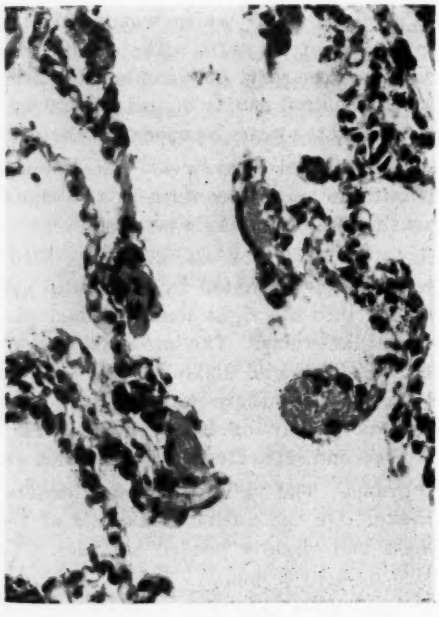


Fig. 1.—Fibrin thrombi, capillaries of lung. (×330.)

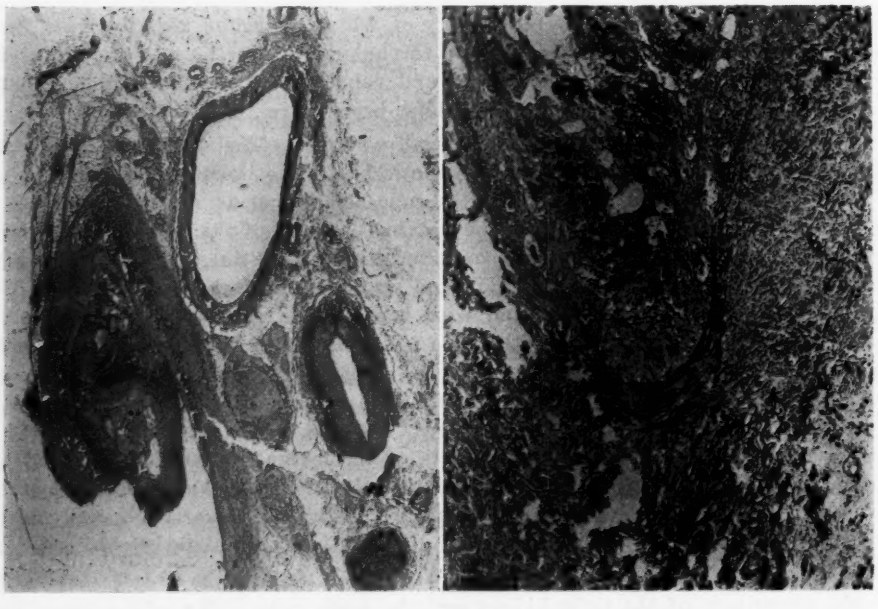


Fig. 2. Fig. 3.

Fig. 2.—Left renal vein, demonstrating extensive fibrin thrombus in process of organization and recanalization. (×5.5.)

Fig. 3.—Left renal vein. Higher magnification of Fig. 2. (×55.)

The striking histologic finding was the presence of multiple widespread thrombotic phenomena, even more extreme than those noted grossly. Although many of the thrombi were of the usual type, consisting of fibrin with enmeshed leukocytes and erythrocytes, there were others composed wholly or predominantly of fibrin. Thus, in the lung, many of the septal capillaries were swollen by rounded discrete fibrillary eosinophilic thrombi (Fig. 1). Others were seen in the renal and hepatic vessels. Many of the larger vessels, including pulmonary, renal, intestinal, uterine, and mesenteric, contained thrombotic masses in which fibrin was the predominant element, and only superficially were agglutinated cellular elements seen.

Fig. 4.—Organizing fibrin thrombus on mitral valve. (×40.)

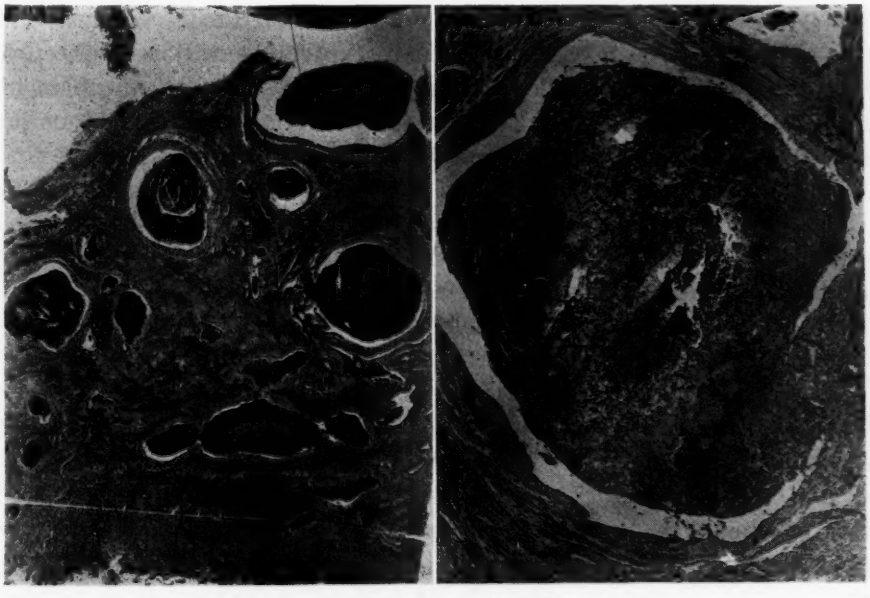


Fig. 5. Fig. 6.

Fig. 5.—Uterine wall showing abnormal, extensive thromboses of vessels. (×5.5.)
Fig. 6.—Higher magnification, thrombus formation, uterine veins. (×30.)

Fibrin thrombi formed vegetative masses on the pulmonary artery and mitral valve. These were not associated with underlying pathologic changes of prior origin. The thrombus in the renal vein showed considerable organization along its line of adherence as well as recanalization (Figs. 2 and 3). Except for a small area with sparse lymphocytic cell infiltration, the venous wall appeared normal. The pulmonary artery and the mitral valve thrombi also showed fibrous organization (Fig. 4). The thrombi of the uterine vessels showed varying degrees of organization, for the most part slight in extent. Many of the "fibrin emboli" in the capillaries of the lung had the linear arrangement in the direction of flow, described by Schneider.[5, 11] Many of the parenchymal thrombotic lesions were associated with acute infarction, viz., lung, kidney, ileum.

The uterine thromboses were unusually advanced and extensive (Figs. 5 and 6). Much of the endometrium itself consisted of necrotic and hemorrhagic gestational decidua. Other endometrial elements, consisting of some flattened secretory glandular epithelium, were seen.

Other lesions, noted in the lung, consisted of areas of edema, some of which were hemorrhagic areas of atelectasis and areas of low-grade, acute interstitial pneumonitis.

Final Pathologic Diagnoses.—

Serosanguineous ascites; thromboses of mesenteric veins, left renal vein (with organization and canalization), inferior vena cava, right common iliac vein, pulmonary artery (with early organization and adherence), hepatic capillaries; organizing fibrinous vegetation on mitral valve; pulmonary edema, multiple acute infarctions; atelectasis; focal acute interstitial pneumonitis; extensive gangrene of ileum; multiple bilateral renal infarction; extensive venous thromboses of uterine wall; old infarction, inferior left parietal lobe of the brain.

Summary and Conclusions

"Fibrin embolism," a pathologic process occurring in human pregnancy, has recently been described. It may well be that this process is responsible for some of the later complications which have previously been described as "hemorrhagic diathesis of pregnancy," obstetrical shock, cardiac failure, and pulmonary edema.[5] This process most often occurs during the last trimester of pregnancy and is seen especially in premature separation of the placenta. It has been amply shown that both the human decidua and the placenta are very rich in thromboplastin.[17] In certain of the abnormalities of human pregnancy, most especially abruptio placentae, excessive amounts of thromboplastin are forced into the peripheral circulation and the formation of fibrin from fibrinogen is initiated. This produces the so-called "fibrin embolism," a disseminated deposition of fibrin, which may, if extensive, cause occlusion of circulation. Such occlusions are most often microscopic in character and must not, despite terminology, be confused with the ordinary types of emboli or thrombi. In the extreme, however, fibrin depositions may be so extensive as to occlude vital organs and the patient may literally clot herself to death.

However, there is a paradox to this, for should the patient survive the fibrin formation, the chemical processes initiated may have quantitatively consumed all circulating fibrinogen with a resultant fibrinopenia and, consequently, failure of the clotting mechanism. The patient is now placed in jeopardy because of the possibility of hemorrhage, especially at parturition.

We cannot assert with certainty that Case 1 represents an instance of hemorrhage based on fibrinopenia. However, in retrospect, this seems highly

probable. This case, nevertheless, alerted us to the possibility of such a mechanism in future cases, particularly since it coincided with the reports of the fundamental work by Reid[9] and Seegers and Schneider.[18] With this background, we were prepared to accept and study thoroughly our second case. This case dramatically exemplifies the evolution of events so clearly described by Schneider, more particularly, the stage of fibrin embolism.[5, 11]

The pathologic findings in our case appear, in basic respects, similar to those of fibrin emboli noted by Schneider, particularly in their predominant fibrin content, their presence in the capillaries of the lungs and liver and the linear arrangement of the fibrin threads. However, in our case, the intravascular thrombosis is more extensive than in previously reported cases, particularly in its involvement of the larger vessels, especially on the venous side: the pulmonary artery, the renal vein, the inferior vena cava, and the superior mesenteric vein. The presence of vascular thromboses in the vessels of the uterine wall is unique. Another unusual feature is the presence of fibrosing, adhering organization of the thrombi in the pulmonary artery, on the mitral valve cusps, and in the vessels of the uterine wall. In the renal vein this has advanced to recanalization. This latter observation indicates a chronicity or the residual evidences of previous episodes.

Not only does this second case confirm Schneider's observations, but it extends our experience with this syndrome. As observed in this instance, it is evident that simple termination of the pregnancy is no longer a guarantee of the cessation of the pathologic process. There still remains the possibility, as this case demonstrated, of a focus of thromboplastin remaining in an abnormal, necrotizing decidua adherent to an old retroplacental site. The normal postpartum involution of the uterus may act to force this thromboplastic material into the peripheral circulation with a resultant continuation of the thromboembolic phenomena. It is clear, therefore, that effort must now be made to develop the diagnostic methods, both laboratory and clinical, and to define the criteria, whereby the decision concerning the extent of intervention may be determined in similar instances encountered in the future.

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1930 PINE STREET

Discussion

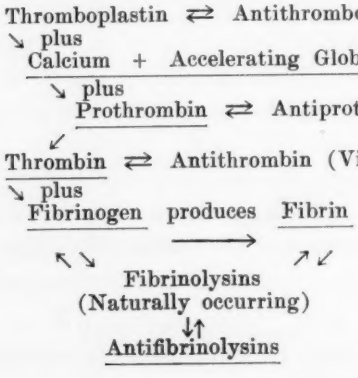
DR. L. A. ERF.—The authors of this paper are to be congratulated for presenting the subject of "fibrin embolism" so clearly. Schneider was perhaps the first to show the practical consequence of premature separation of the placenta upon the blood-clotting mechanisms in animals and human beings. The tissue breakdown products plus the clotted blood which are found within the uterus in abruptio placentae contain large amounts of the coagulant named thromboplastin (and quite often large amounts of fibrinolysins and hemolysins). During the contractions of the uterus thromboplastin is squeezed into the circulation and thereby causes intravascular clotting which if extensive can result in fibrin emboli and death. If the intravascular clotting is slow enough and extensive enough, all of the fibrin can be precipitated, resulting in fibrinopenia, and therefore paradoxically can cause extensive bleeding. Such noncoagulable blood due to loss of fibrinogen is the same as "whipped" blood, which decades ago was given as transfusion. Schneider thinks that this same intravascular clotting mechanism can also be responsible for eclampsia, particularly when the fibrin emboli lodge in the liver in large numbers. A somewhat simliar mechanism occurs during menstruation since menstrual blood (or fluid):

1. Does not clot. Menstrual blood has already been clotted in the uterus by the local thromboplastin and only the "whipped" or fibrinopenic hemorrhagic fluid is released. The fibrin has to be precipitated and degenerated and then discharged vaginally.
2. Has elevated thromboplastin levels. Menstrual fluid accelerates the clotting of normal blood.
3. Often has elevated fibrinolysin levels also.
4. Occasionally has elevated levels of hemolytic substances too.

The subject of thrombosis is important in every field of medicine. Perhaps the most common cause of death physiopathologically is thrombosis-cerebral thrombosis, coronary thrombosis, phlebothrombosis, renal thrombosis, pulmonary thrombosis, many of which occur because arteriosclerosis destroys the endothelial lining of these blood vessels and permits clotting of blood intravascularly. Thrombosis is usually a result of too much or of too little of some of the enzymes or proteins which enter into the process of clotting. Conversely, bleeding is likewise a result of too much or too little of the antagonists of the above agents.

Coagulation at present is thought to occur in three phases: Phase I, liberation or production of thromboplastin; Phase II, conversion of prothrombin to thrombin; Phase III, precipitation of fibrin from fibrinogen.

Howell's theory which has been modified only slightly during the past 40 years can be diagrammatically illustrated as follows:



If there is an excess of any of the agents that are underlined, thrombosis can occur if there is a deficiency of these agents, then bleeding can occur. If there is an excess of any of the agents that are not underlined, bleeding can occur; if there is a deficiency of these agents, thrombosis can occur. Nearly all of these substances can be purchased in nearly ''pure'' (uncontaminated) form. Quick believes thromboplastin is produced by the combination of thromboplastinogen of the plasma with thromboplastinogenase of the platelets. Quick believes hemophilia is due to an inherited deficiency of plasma thromboplastinogen; Brinkhous believes it is due to lack of the platelet enzyme (thromboplastinogenase); and Tocantins believes it is due to excessive amounts of antithromboplastin. The laboratory data of Tocantins seem the most convincing at present. Presumably the ''hemophilia of pregnancy'' is due to an excess of antithromboplastin; while an excess of thromboplastin is the cause of ''fibrin emboli'' which is the subject under discussion tonight. The tests performed by Dr. Weber and associates indicated an excess of thromboplastin in his case.

The other agents on the chart can be briefly discussed as follows:

1. Decreased levels of prothrombin can be due to a congenital disease or can be due secondarily to infections, liver disease, vitamin K deficiency, or Dicumarol, salicylate or penicillin intoxication, etc.

2. Antithrombins such as vitamin E and heparin have been used by Oschner to prevent postoperative phlebothrombosis.

3. Fibrinogenopenia may occur due to a congenital defect or to overutilization of the fibrinogen as occurred in the case presented tonight.

4. Fibrinolysins occur naturally and are also produced by various bacteria. The naturally occurring variety are those that ''unclot'' cadaver blood so that it can be used for transfusions. Those produced by bacteria are often instilled into patients with empyemia, hemothorax, etc., in order to ''dissolve'' the fibrin and thereby encourage drainage. Increased levels of fibrinolysins occur not uncommonly in women with Rh-negative blood who have intrauterine fetal deaths; and this results in severe postpartum bleeding.

5. Excessive anticoagulants such as hyperheparinemia occur in leukemia, after x-radiation, etc., and can usually be overcome by protamine (antiheparin).

6. Combinations of any of the above disorders (excessive quantities or deficiencies) can occur; and we must admit that there are many factors in the mechanism of blood coagulation (platelet enzymes, endothelial enzymes, tissue enzymes, plasma enzymes, etc.) that we do not understand.

At this point it can easily be seen that postpartum bleeding can be a result of many mechanisms and that fibrinogen (which can be isolated by Cohn's blood fractionation methods) therapy as stressed by Reid and Schneider is not the answer for all of the bleeding problems but only for those in which a deficiency of fibrinogen exists. In most cases of abnormal postpartum bleeding, the treatment of choice is multiple transfusions of blood, since fluid blood is well balanced for all of the agents diagrammed above. Since it is now known that the uterus is the site of excess amounts of thromboplastin, hysterectomy must be seriously considered in such cases as presented tonight. And I would like to ask the clinicians:

1. Would you not seriously consider hysterectomy in the next similar case?

and the pathologist:

2. Are any of the emboli older than 14 days?

In answer to Dr. Thaddeus Montgomery's question as to which type of blood—fresh or citrated—would be preferable in such cases as was presented tonight, I can say that presumably citrated blood has only its calcium immobilized and that the other agents needed in the clotting mechanism are unaltered. Therefore, I doubt if fresh blood is superior to citrated blood in the vast majority of instances of bleeding of this type.

DR. D. R. MERANZE.—In reply to Dr. Erf's question, I cannot state with certainty whether any of the thrombi are older than 14 days. What can be stated is that, judging

by their character and their varying degrees of organization, they are of different ages. It may, therefore, well have been that thrombosis had been proceeding more or less continuously from the time of delivery to the time of death.

DR. WEBER (Closing).—We are quite aware that transfusion is the treatment par excellence for these clotting abnormalities. Accordingly we saved the first patient by giving her 6,500 c.c., probably completely replacing her blood with donor blood, as it were.

The second case, from the dramatic onset of the cerebral accident, unfolded itself before our very eyes. With the aid of a competent laboratory we were able to study her completely. We corresponded with Dr. Schneider and agreed that emptying of the uterus would terminate this abnormal process. We now feel differently. We do think, Dr. Erf, that hysterectomy might have saved this patient's life. It is our thesis that, during the fourteen postpartum days, the normal involution of the uterus daily forced into the peripheral circulation small amounts of thromboplastin from the abnormal, necrotizing decidua. This substance brought about intravascular blood coagulation so that the patient actually clotted herself to death. Cesarean hysterectomy, we believe, might have saved her.

A TEN-YEAR ANALYSIS OF BREECH DELIVERIES, 1939-1948

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THE purpose of this paper is to present an analysis of the treatment of breech presentations in the Sloane Hospital for Women for the years 1939 through 1948, inclusive.

In addition, this paper is a plea for the standardization of criteria as to what constitutes a normal uncomplicated breech delivery and what hazards should be logically included or excluded. As stated by Guyer and Heaton,[22] it is evident that we cannot compare fetal mortality rates from different clinics unless the standards are the same. Their paper on "The Fetal Risk in Breech Delivery" seemed to us the most comprehensive, and this analysis is modeled on it.

Herein we attempt to analyze 658 cases of primary breech presentation which occurred in the Sloane Hospital for Women from January, 1939, to January, 1949. This figure includes the 60 cases of cesarean section which are later analyzed separately. Internal podalic versions followed by breech extractions are not included. During this period there was a total of 17,096 deliveries, giving a breech incidence of 3.86 per cent. All patients were delivered by the resident staff with the assistance of an attending obstetrician if difficulties were anticipated.

The methods of delivery were defined as follows:

"(a) *Spontaneous breech delivery,* a term used for the cases in which the breech is quickly and spontaneously delivered without any manipulation by the doctor. This usually occurs only with small babies. (b) Assisted breech delivery, in which the birth is allowed to proceed spontaneously up to the appearance of the umbilicus, after which assistance is given for the delivery of the shoulders and head. This is the usual procedure for breech delivery on the service unless definite indications exist for breech extraction. Both shoulders are delivered anteriorly if possible, but, if difficulty is encountered, the posterior shoulder is delivered as such. The after-coming head is delivered by either the Mauriceau-Smellie-Veit or Wigand maneuver. If these fail, Piper forceps are used. (c) Breech extraction, in which the operative interference is commenced before the passage of the breech over the perineum. The procedure is carried out on this service only for specific indications, the chief one being prolongation of the second stage."

Analgesia was usually Seconal and scopolamine although in the last few years Demerol has either replaced Seconal or been added to the other two. Nitrous oxide and oxygen with or without the addition of ether was used for the second stage.

†Deceased.

Only a small percentage of cases were admitted from other than the service's antepartum clinic, and x-ray pelvimetry by the Caldwell-Moloy technique was very frequently employed.

External version is the accepted policy at this hospital and during these years a total of 368 versions were done. Of these cases, 277, or 75.3 per cent, subsequently delivered as vertex presentations. Sixty-nine, or 18.7 per cent, subsequently delivered as breech presentations. Twenty-two, or 6 per cent, were delivered by other means, such as cesarean section. There were eight cases in which fetal death occurred and in which either successful version or unsuccessful attempts followed by spontaneous version might possibly have been the cause of death. In only one of these did it seem probable that the version was responsible. In this case the fetal heartbeat was heard immediately after the version, but was not heard again. The patient delivered a macerated fetus three weeks later and a true knot was found in the cord. In the other cases there were complicating factors such as toxemia, transverse presentations, face presentations, medium-forceps delivery, and Braxton Hicks version.

TABLE I. CALCULATION OF CORRECTED FETAL MORTALITY RATE IN BREECH DELIVERY, 1939-1948

	CORRECTIONS	NO. OF CASES	STILLBIRTHS AND NEONATAL DEATHS	TOTAL NO. OF CASES	TOTAL STILLBIRTHS AND NEONATAL DEATHS	FETAL MORTALITY RATE, PER CENT
Totals				598	122	20.4
	Non-Viable	61	53			
Remainder				537	69	12.8
	Premature	92	33			
Remainder				445	36	8.1
	Macerated	9	9			
Remainder				436	27	6.2
	Congenital defects	7	7			
Remainder				429	20	4.7
	Premature separation of placenta	1	1			
Remainder				428	19	4.4
	Placenta previa	1	1			
Remainder				427	18	4.2
	Twins	80	0			
Remainder				347	18	5.2
	Prolapse of cord	12	3			
Remainder				335	15	4.5
	Pre-eclampsia and eclampsia	1	0			
Remainder				334	15	4.5
	Hemorrhagic disease of newborn					
Remainder						
	Icterus gravis					
Remainder						
	Miscellaneous	3	3			
Final Remainder				331	12	3.6

In one case of cesarean section the patient had a known borderline pelvis and was allowed a trial labor which came more or less to a standstill, but the deciding factor for doing the cesarean at that time was an irregular fetal heartbeat. She would probably have had a section after more labor but at operation the cord was found to be around the neck.

TABLE II. PROLAPSED CORD IN VERTEX PRESENTATION, 1939-1948

1. Number of cases			49
2. Number of living children			33 (67.4%)
3. Number of stillbirths			11 (22.4%)
4. Number of neonatal deaths			5 (10.2%)
5. *Parity.*—		*Mortality.*—	
Primiparas	20	4	(20%)
Multiparas	29	12	(41%)

6. *Method of Delivery and Mortality.*—

	NORMAL SPONTANEOUS	LOW FORCEPS	MEDIUM FORCEPS	VERSION AND BREECH	CESAREAN SECTION
Method of delivery	17	8	11	12	1
Mortality—uncorrected	8(47.0%)	0	3(27.2%)	5(41.6%)	0
Term babies	7	0	3	3	0
Mortality corrected	41.1%	0	27.2%	25.0%	0

TABLE III. CORRECTED FETAL MORTALITY RATE IN PRIMIPARAS AND MULTIPARAS

	PRIMIPARAS		MULTIPARAS	
	NO. OF CASES	STILLBIRTHS AND NEONATAL DEATHS	NO. OF CASES	STILLBIRTHS AND NEONATAL DEATHS
Spontaneous breech delivery	23	0	21	1
Assisted breech delivery	142	1	102	1
Breech extraction	30	7	13	2
Totals	195	8	136	4
Corrected fetal mortality rate	4.1 Per Cent		2.94 Per Cent	

Complications of Breech Delivery

In this series, exclusive of cesarean sections, there were 598 breech deliveries with 122 stillbirths or neonatal deaths, giving a gross fetal mortality rate of 20.4 per cent. Our analysis of these 122 deaths appears in Table I. We have used the same method and table as Guyer and Heaton but have slightly altered the sequence. In calculating the risks of breech delivery we have excluded the same complicating factors, namely:

1. "Nonviability-Nonviable infants are defined on this service as infants born before the twenty-eighth week of gestation and weighing less than 3 pounds" (1,362 grams).

2. "Prematurity-A premature birth is defined on this service as occurring between the twenty-eighth and thirty-eighth weeks of pregnancy, the infant weighing between 3 and 5 pounds" (1,362-2,270 grams).

3. Nine macerated term stillborn infants were eliminated from this series. In three of these the mother had definite toxemia without placental separation; three had the cord around the neck or shoulders or both; and three had no discernible cause.

4. Seven cases of congenital defects incompatible with life were excluded. These were: three hydrocephalics; two anencephalics; one with achondroplasia; and one with eventration of abdominal viscera.

TABLE IV. ANALYSIS OF TWELVE UNCOMPLICATED BREECH FETAL DEATHS

PARITY	BIRTH WEIGHT (GRAMS)	PELVIS			TYPE OF DELIVERY	RESULT TO BABY	AUTOPSY	COMMENT
		X-RAY	TYPE	MEASUREMENTS (CM.)				
P.	3,275	Yes	Large gynecoid	A.P. 13.5 Trans. 14.9	Assisted	Intrapartum stillbirth	Laceration of right tentorium cerebelli, complete; right subdural hemorrhage; congenital intrauterine lobar pneumonia (?)	No disproportion. Premature rupture of membranes, 7 days. Delivery not difficult
M.	3,544	No	Gynecoid	——	Assisted	Stillbirth	Congenital atelectasis of lungs; aspiration of amniotic fluid, slight; laceration of tentorium, bilateral, incomplete; intracranial hemorrhage, subdural; spinal meningeal hemorrhage	Rh incompatibility. Cord twice around neck and once around body. No disproportion
P.	2,948	No	Slightly under average gynecoid with some anthropoid tendencies	——	Extraction	Stillbirth	Laceration of tentorium, bilateral; intracranial hemorrhage, subdural, supratentorial; congenital atelectasis of lungs; spina bifida occulta	No disproportion. Easy delivery, 6½ hours
P.	3,345	Yes	Anthropoid	A.P. 12.3 Trans. 12.6	Extraction	Stillbirth	No autopsy	Moderate disproportion. Impacted shoulders, extended arms. Outlet arrest
M.	3,430	Yes	Anthropoid	A.P. 12.3 Trans. 12.6	Extraction	Stillbirth	Aspiration of amniotic fluid; subcapsular hematoma of liver; hemorrhages in adrenal, right, and abdominal wall	Slight disproportion; difficulty with shoulders and arms
M.	3,500	No	Gynecoid	——	Spontaneous	Neonatal death	Laceration of tentorium; incomplete, left; intracranial hemorrhage; aspiration of amniotic fluid; congenital atelectasis of lungs; congenital malformation of heart	Pre-eclampsia. No disproportion. Excessive sedation
M.	4,082	No	Gynecoid	——	Extraction	Neonatal death	Laceration of tentorium, bilateral; intracranial hemorrhage; congenital atelectasis of lungs; fracture of clavicle	No disproportion. Uterine inertia. Premature rupture of membranes, 38 hours. Prolonged labor, 38 hours

P.	2,470	Yes	Gynecoid	A.P. 12.6 Trans. 12.7	Extraction	Neonatal death	Intracranial hemorrhage; hematoma of sterno-cleidomastoid muscle, left	Pre-eclampsia. No disproportion
P.	2,690	Yes	Platypelloid	A.P. 10.8 Trans. 12.6	Extraction	Neonatal death	Laceration of tentorium, right complete, left incomplete; subdural hemorrhage; laceration of subarachnoid space	Moderate disproportion. Difficult forceps on after-coming head. Premature rupture of membranes, 5 days. Incompletely dilated cervix
P.	3,005	Yes	Gynecoid with flat tendency	A.P. 10-10.5 Trans. 13.5	Extraction	Neonatal death	Laceration of tentorium, bilateral; subdural hemorrhage; congenital pneumonia; meningeal spinal hemorrhage; aspiration of meconium	No disproportion. Prolonged labor, 70 hours. Premature rupture of membranes, 70 hours (?). Delivery easy. Primary uterine inertia
P.	3,350	Yes	Anthropoid	A.P. 11.5 Trans. 11.5	Extraction	Neonatal death	Bilateral tentorial tears, incomplete; subdural hematoma; atelectasis; lobar pneumonia, bilateral, early	Considerable disproportion by x-ray. Mild toxemia ante partum and second-degree anemia, clinically. Pelvis ok. Nuchal hitch. Two loops of cord around neck tightly. Head delivered easily. Labor 27½ hours, membranes ruptured 28 hours
P.	3,755	Yes	Gynecoid	A.P. 12 Trans. 14.5	Extraction	Stillbirth	Aspiration of amniotic fluid; congenital pneumonia; congenital atelectasis of lungs; laceration of tentorium, bilateral	Pelvis adequate for delivery by x-ray. Prolonged labor, 37 hours. Premature rupture of membranes, 38 hours. Easy extraction. Intrapartum pyrexia, 102.8° F. Intrapartum death. Cord not pulsating during extraction

5. There was but one case of premature separation of the placenta and in this there was a fatal result in the baby, and one case of placenta previa resulting in a stillbirth, exclusive of those in which cesarean section was done.

6. *Twins*—because of the hazards inherent in the very fact of a twin pregnancy.

7. *Prolapse of Cord:* There were 29 prolapsed cords in 598 cases, an incidence of 4.85 per cent. There were 12 prolapsed cords among single viable mature infants without placenta previa or premature separation of the placenta, an incidence of 3.46 per cent. There were three stillbirths or neonatal deaths. One cesarean section was done for prolapsed cord and fibroids. Two were stillborn and one died in the neonatal period, and all the fatalities were felt to be due to the asphyxia. They occurred in the years 1941, 1945, and 1946.

8. Only one case of pre-eclampsia was eliminated and in this a live baby was obtained.

9. No cases of severe hemorrhagic disease of the newborn or icterus gravis were encountered.

10. Miscellaneous causes accounted for the elimination of three cases in all of which the baby was lost. One of these infants died of peritonitis due to a perforation of a gangrenous volvulus, another of peritonitis due to necrosis and perforation of the stomach with a congenital absence of the gall bladder. The third had anasarca, ascites, bilateral hydrothorax, atelectasis of the right lung, and congenital malformation of the right kidney and ureter.

During the years of this study there were 15,757 vertex deliveries (excluding births of nonviable infants) with 49 prolapsed cords, an incidence of 0.31 per cent. This figure makes the occurrence of prolapsed cord in breech deliveries about ten times as frequent as in vertex deliveries. Of the 49 cases, 43 were term, 5 premature, and one previable.

The mortality from prolapsed cords in 347 term breech presentations was 3 in 12 cases, an incidence of 25.0 per cent. In term vertex presentations it was 13 in 43, an incidence of 30.2 per cent. This is not in agreement with the finding that prolapsed cords in vertex presentations are a much more serious complication than in breech presentation. Table II shows a breakdown of the cases of prolapsed cord in vertex presentation.

Fetal Mortality Rate According to Parity

A comparison of the corrected fetal mortality rates in primiparas and multiparas is shown in Table III.

Eight fatalities occurred in the 195 primiparas and seven of these were in cases in which extractions were done. In the four fatal cases in 136 multiparas there were one spontaneous, one assisted, and two breech extractions. The essential cause for these may be either in the operation itself or in the reason that the operation for breech extraction was necessary.

Fetal Mortality Directly Due to Breech Delivery

There were in this series 12 cases of fetal death in uncomplicated breech deliveries. Table IV shows the breakdown of these cases.

Four of the twelve cases did not have x-rays. Three patients were multiparas. In only one of these was there finally considered to be any disproportion, but the assisted breech delivery of a stillborn 6½ pound baby was clinically considered to be easy. However, an autopsy on the infant showed definite intracranial injury. Another mother had some Rh incompatibility, the cord was

twice around the neck and once around the body, and the child was stillborn, but again the autopsy showed evidence of intracranial injury as well as atelectasis of the lungs and some aspiration of amniotic fluid. The mother of the third infant, who died in the neonatal period, had pre-eclampsia and was thought possibly to have been excessively sedated, but the autopsy on the infant showed an incomplete tentorial laceration as well as atelectasis and aspiration of amniotic fluid. The mother of the fourth infant, who also died in the neonatal period, had uterine inertia, premature rupture of the membranes, a prolonged thirty-eight hour labor which finally necessitated Dührssen's incisions and, as might be expected, autopsy showed intracranial injury and a fractured clavicle in the infant.

Only one of the twelve cases did not have an autopsy.

There were two assisted breech deliveries; nine breech extractions; and one spontaneous delivery. The latter was in the case of the previously mentioned pre-eclamptic patient who was excessively sedated but yet showed intracranial injury. There were six stillbirths and six neonatal deaths.

Nine infants showed lacerated tentoria and other signs of intracranial injury. One showed intracranial hemorrhage without tentorial laceration and another aspiration of amniotic fluid, a subperitoneal hematoma of the liver, and hemorrhages in the right adrenal and abdominal wall. In this case there had been difficulty with the arms and shoulders during delivery.

In four cases there was thought to be slight to moderate disproportion by x-ray and in one case not x-rayed there was thought to be slight disproportion clinically, but the delivery was considered easy.

Four patients had a labor of over twenty-four hours.

Six patients had premature rupture of membranes, anywhere from 28⅓ hours to seven days. In three of these, delivery was considered easy and the other three had a variety of the usual complications, such as double nuchal hitch, etc.

Four of the patients were multiparas and eight primiparas. One of the four multiparas had an assisted breech delivery, one spontaneous, and two extractions. Seven of eight primiparas had breech extractions, and one an assisted breech delivery.

In our series, we had 60 cases of cesarean section in breech presentations, of which 29 were done for disproportion and no other reason.

TABLE V. TOTAL NUMBER OF CESAREAN SECTIONS, 1939-1948, WITH BREECH PRESENTATIONS EQUALED 60

Major indications for cearean section.—	
Cephalopelvic disproportion	29
Previous cesarean section	12
Placenta previa	7
Uterine inertia	4
Previous vaginal plastic	2
Premature separation	1
Prolapsed cord	1
Brain tumor	1
Diabetes	1
Fibrosarcoma of sacrum	1
Elderly primipara with pre-eclampsia	1

The one maternal death—in 1941—was in a patient on whom cesarean section was done for cephalopelvic disproportion.

The major indication for these operations is shown in Table V and the breakdown in Table VI. As can be seen from the table, the greatest number of cesarean sections were done for cephalopelvic disproportion, and most of those

TABLE VI. ANALYSIS OF CESAREAN SECTIONS IN BREECH PRESENTATIONS, 1939-1943

PARITY	BIRTH WEIGHT (GRAMS)	PELVIS			RESULT TO BABY	INDICATION
		X-RAY	TYPE	MEASUREMENTS (CM.)		
P	2,880	Yes	Gynecoid-anthropoid	A. P. 10.5 Trans. 11.5	Normal	Twelve hour trial of labor. Under average in size
M	4,050	Yes	Large gynecoid with narrowing of forepelvis	--	Normal	Previous cesarean section
P	1,240	No	Not determined. ? Gynecoid	--	Neonatal death	Placenta previa
M	3,620	Yes	Moderate-sized android	--	Normal	Previous cesarean section
P	4,020	Yes	Small gynecoid-android	A.P. 10.75 Trans. 12.6	Normal	Membranes ruptured 14 hours; 14 hour trial of labor
P	3,610	Yes	Android-gynecoid	--	Normal	Pregnancy postmature; obesity; premature rupture of membranes. Maternal death
M	2,780	Yes	Android with considerable narrowing	--	Normal	Cephalopelvic disproportion for this pelvis and breech presentation
P	3,500	Yes	Android, flat	--	Normal	Premature rupture of membranes, android pelvis, breech position
P	2,670	No	Flat android	--	Normal	Brain tumor
M	3,630	Yes	Android	A.P. 10.3 Trans. 13.2	Normal	Android pelvis; high degree of disproportion
P	4,520	Yes	Platypelloid	--	Normal	High degree of disproportion
P	3,420	Yes	Android-gynecoid	A.P. 10.0 Trans. 12.3 Inters. diam. 10.0	Normal	Absolute disproportion
P	3,250	Yes	Android	--	Normal	Fibromyoma; diabetes mellitus; cephalopelvic disproportion
M	2,500	No	Gynecoid	--	Neonatal death	Placenta previa
P	3,080	Yes	Rachitic flat	A.P. 8.5 Trans. 12.5	Normal	High degree of disproportion
M	3,900	No	Gynecoid	--	Normal	Severe diabetes mellitus
P	2,700	Yes	Gynecoid with forward lower sacrum and prominent spines	A.P. 12.0 Trans. app. 14.0	Normal	Moderate disproportion. Forward lower sacrum would obstruct unmolded head
P	4,030	No	Gynecoid	--	Normal	Fibrosarcoma of sacrum
P	2,170	Yes	Asymmetrical gynecoid, flat; ample	A.P. 13.0 Trans. 13.5 Inters. diam. 11.0	Normal	Elderly primipara. Pre-eclampsia, mild
P	3,150	Yes	Gynecoid with flat tendency	A.P. 10.8 Trans. 12.2	Normal	Borderline disproportion. Premature rupture of membranes, 6 hour trial of labor

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P	3,150	Yes	Gynecoid with slightly narrowed subpubic arch	A.P. 12.5 Trans. 13.5	Normal	Elderly primigravida. Uterine inertia
P	4,050	Yes	Android	A.P. 10.5 Trans. 12.5 Inters. diam. 8.5	Normal	Cephalopelvic disproportion for breech presentation. Membranes ruptured 17 hours
M	3,530	Yes	Gynecoid	A.P. 12.0 Trans. 13.0	Normal	Cephalopelvic disproportion
M	Twins A, 2,050 B, 2,110	Yes	Anthropoid	A.P. 12.0 Trans. 13.0 Inters. diam. 10.0	Neonatal death	Two previous cesarean sections
M	3,170	No	Small gynecoid with anthropoid tendencies	--	Normal	Two previous cesarean sections
M	2,910	No	Small anthropoid	--	Normal	Previous cesarean section for cephalopelvic disproportion
P	Twins A, 1,870 (Version) B, 1,580 (Breech)	No	Not determined	--	Normal	Complete placenta previa
M	1,510	No	Rachitic, asymmetrical	--	Stillbirth	Premature separation of placenta
M	3,070	No	Gynecoid	--	Normal	Previous plastic repair
P	2,720	Yes	Small gynecoid	A.P. 9.7 Trans. 12.6	Normal	Cephalopelvic disproportion; 9 hour trial of labor
P	3,780	Yes	Gynecoid-android	A.P. 11.3 Trans. 13.0	Normal	Uterine inertia
M	3,440	No	Android, flat	--	Normal	Previous cesarean section for cephalopelvic disproportion
M	3,210	No	Android	--	Normal	Two previous cesarean sections
M	3,290	No	Flat	--	Normal	Previous cesarean section for toxemia
M	3,800	No	Large gynecoid	--	Normal	Placenta previa
P	3,790	Yes	Gynecoid	A.P. 12.0 Trans. 14.0	Normal	Ruptured membranes 34 hours. Uterine inertia and fibromyomas
P	2,920	Yes	Android, flat	A.P. 9.5 Trans. 12.8	Normal	Cephalopelvic disproportion
P	2,450	Yes	Platypelloid-android	A.P. 9.8 Trans. 13.5	Normal	Disproportion with breech presentation. Cephalopelvic disproportion
P	3,280	Yes	Android-platypelloid	A.P. 11.4 Trans. 13.0	Normal	Cephalopelvic disproportion, fibroids, toxemia
P	3,060	Yes	Small gynecoid	A.P. 10.4 Trans. 12.3	Normal	Borderline pelvis

TABLE VI—CONT'D

PARITY	BIRTH WEIGHT (GRAMS)	PELVIS			RESULT TO BABY	INDICATION
		X-RAY	TYPE	MEASUREMENTS (CM.)		
M	1,800	No	Gynecoid	--	Normal	Placenta previa
M	2,850*	No	Gynecoid	--	Normal	Placenta previa, partial
M	3,610	No	Android-gynecoid	--	Normal	Previous section for cephalopelvic disproportion
M	2,750	No	Ample gynecoid	--	Normal	Previous plastic repair
M	3,665	Yes	Gynecoid-android	A.P. 11.0 Trans. 13.5	Normal	Cephalopelvic disproportion
P	3,025	Yes	Gynecoid with android characteristics	--	Normal	Cephalopelvic disproportion. Fibroids
M	3,300	Yes	Flat	A.P. 11.2 Trans. 15.0	Normal	Three previous sections
P	2,950	No	Anthropoid	--	Normal	Fibroids and prolapsed cord
M	3,610	No	Android-gynecoid	--	Normal	Cephalopelvic disproportion
M	2,980	No	Flat, gynecoid	--	Normal	Two previous sections
P	3,040	Yes	Flat, gynecoid	--	Normal	Cephalopelvic disproportion
M	4,330	Yes	Small gynecoid	A.P. 10.0 Trans. 12.0	Normal	Pre-eclampsia, cephalopelvic disproportion, 10 hour trial of labor
P	3,570	Yes	Anthropoid	A.P. 12.2 Trans. 11.8 Inlet 11.2 Inters. diam. 9.5	Normal	Cephalopelvic disproportion, 11 hour trial of labor
P	2,545	Yes	Small android	A.P. 10.2 Trans. 13.5	Normal	Cephalopelvic disproportion. Dangerous pelvis even for vertex presentation
M	3,725	No	Gynecoid with android sacrum	--	Normal	Placenta previa; ? placenta accreta
P	3,560	Yes	Flat	A.P. 11.5 Trans. 12.0 Inlet 11.3	Normal	Cephaloplevic disproportion; 9½ hour trial of labor
P	2,430	Yes	Flat, gynecoid	A.P. 11.0 Trans. 13.5 Inlet 10.3 Inters. diam. 13.0	Normal	Relative cephalopelvic disproportion. Pre-eclampsia
P	2,675	Yes	Flat, gynecoid	A.P. 10.0 Inters. diam. 11.5	Normal	Cephalopelvic disproportion. Small and poor pelvis even for vertex presentation
M	3,825	Yes	Gynecoid-android†	--	Normal	Cephalopelvic disproportion. Previous cesarean section
P	4,200	Yes	Large anthropoid	A.P. 12.0 Trans. 13.6	Normal	Uterine inertia, cervical dystocia; prolonged labor

*In previous pregnancy (1945) (270944) A.P. 10.7, Trans. 13.0. Marked degree of inlet disproportion.
†Dr. Ball's report: Platypelloid at inlet with gynecoid characteristics at outlet. No report by Obstetrical Dept.

which were done because of previous cesarean section also had disproportion as a major reason for their original section. Placenta previa was next highest with seven cases; uterine inertia next; and finally eight cases for assorted reasons. Twenty-three of the 60 patients were not x-rayed, but in only one of these was disproportion the essential reason for the section. The other reasons included placenta previa, premature separation, previous cesarean section, etc.

There were four fetal deaths among the cesarean sections. One was in a patient with central placenta previa with pyrexia of unknown origin who was operated upon at 24 weeks' gestation, resulting in a neonatal death due to prematurity. The second was a complete separation of the placenta at 32 weeks' gestation. The third was a central placenta previa at 28 weeks with neonatal death due to prematurity and congenital atelectasis; and the fourth, twins at 33 weeks, weighing 2,050 and 2,110 grams, respectively, who died within 24 hours and who at autopsy showed atelectasis only.

There was one maternal death in this series whose autopsy showed acute purulent endo- and myometritis; acute fibrinopurulent pelvic peritonitis; bilateral lobular pneumonia; and the general signs of an overwhelming sepsis. The outstanding organism found in anaerobic cultures of the uterus and lung was *Cl. welchii.* This death occurred in 1941 on the fourth postoperative day and the patient received no antibiotics. The main indication for section in this patient was a borderline disproportion. This was unquestionably an obstetrical death, but there was very adequate indication for the section; and perhaps if she had appeared on the scene a few years later we would have been better prepared to combat her sepsis.

Summary and Conclusions

1. Since it is apparent from the autopsy findings in the twelve fetal deaths after uncomplicated breech delivery that breech delivery even of the spontaneous variety is a traumatic procedure, every effort should be made either to correct this position or to employ cesarean section when labor deviates in even slight degrees from normal. This includes not only slight degrees of pelvic disproportion but also such variants as premature rupture of the membranes with inertia or prolonged labor.

2. To accomplish this, the diagnosis of fetal position during the antepartum course should be most carefully made and external version insisted upon.

3. By employing cesarean section for cephalopelvic disproportion in 29 cases as against Guyer and Heaton's 16 cases, we were able to reduce the fetal mortality by slightly less than 1 per cent.

4. The operation of breech extraction is a formidable procedure from the baby's point of view and should not be undertaken lightly.

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ABDOMINAL PREGNANCY

Report of Five Additional Cases

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THE incidence of abdominal pregnancy varies considerably in the different reports. Quilliam[1] estimates that all types of ectopic gestations occur in one of every 2,750 gynecological admissions requiring surgery. He also estimates that one abdominal pregnancy occurs in every 12,500 pregnancies of all types seen in hospital practice. In December, 1951, Burleson and Bragg[2] reported two cases of full-term abdominal pregnancies seen in the Decatur General Hospital, one of the babies being a normal infant who is still alive. The five cases presented in this report will make a total of seven cases seen in the Decatur General Hospital during a five-year period, since Jan. 1, 1947. During this period the incidence of all ectopic gestations was as follows: ruptured tubal pregnancy, 5; intact tubal pregnancy, 7; primary ovarian pregnancy, 1; abdominal pregnancy, 7.

The incidence of all ectopic pregnancies to total pregnancies in the hospital was 1 to 100. The incidence of abdominal pregnancies to total pregnancies was 1 in 286. The incidence of abdominal pregnancies to total gynecological operations was 1 to 134. The incidence of abdominal pregnancies to total live births was 1 to 261.

The signs and symptoms of ectopic pregnancy have been excellently covered in the literature by McNeile,[3] Jarcho,[4] Cross,[5] and others. It will be noted that the classical signs and symptoms of ectopic pregnancy are usually present in those cases generally regarded as secondary, but the symptoms are quite variable in regard to those cases recognized as primary.

Case 1.—(24568) Mrs. F. H., white, aged 27 years, para i, gravida ii, reported to the office on April 8, 1947, with a chief complaint of constant nausea and vomiting, continuous backache, a painful mass in the lower abdomen, frequency of urination and pain in the right lower quadrant of the abdomen following urination. She had lost 20 pounds since Jan. 1, 1947. Her family history and past history were noncontributory. There had been no serious illnesses, injuries, or operations. She had given birth to a normal child on Jan. 30, 1945, after a normal pregnancy and labor.

The patient's last normal menstrual period occurred on Dec. 14, 1946. The only sexual intercourse the patient had had in approximately two months occurred on Dec. 28, 1946. No sexual contacts had been made since that time. On Jan. 1, 1947, the patient had a uterine suspension and incidental appendectomy. She made a satisfactory recovery from the operation, but two weeks after the surgery she developed nausea and vomiting which became progressively more severe, accompanied by a bloody vaginal discharge. On re-

porting back to her physician, she was again hospitalized and given Ergotrate, for an incomplete abortion. The nausea and vomiting continued and on Feb. 26 a dilatation and curettage were performed. Following this she felt better for a few days, but within a week's time the nausea and vomiting recurred and she was readmitted to the hospital and given a course of penicillin with continued Ergotrate tablets. Because the symptoms persisted, on March 24, she was given the second dilatation and curettage. It is interesting to note that at no time was there any severe, lancinating or cutting pain, no urgency or tenesmus of the bladder or bowels, and no syncope.

When the patient reported to me on April 8, 1947, she was obviously sick. She showed evidence of considerable recent weight loss and general weakness. Physical examination revealed a fairly firm mass extending 13 cm. above the symphysis. This was not freely movable, nor was it tender on palpation. The cervix was cyanotic, firm, normal in size, and apparently healthy. On bimanual examination, the uterus was difficult to outline and no line of demarcation between the suprapubic mass and the uterus was made out. There was extreme tenderness in the right adnexal region and movement of the cervix would cause a slight motion of the suprapubic mass. Laboratory work showed secondary anemia, normocytic type. The patient was Rh positive, her nonprotein nitrogen, serum protein, and fasting glucose were all within normal limits. In view of the history given by the patient and the physical findings, it was felt that a laparotomy should be performed in the immediate future and the patient was so advised. Since the patient's parents lived in a nearby city which contains a prominent teaching institution, the patient was referred, at her request, to a consultant in obstetrics and gynecology for his care. She remained in a hospital under the care of the consultant for a period of two weeks during which time exhaustive tests were made. Following this she was discharged with the diagnosis of a normal pregnancy, and told to go ahead with her pregnancy and then have her baby normally.

The patient was seen again by me on Aug. 22, 1947. She stated that she had been fairly well throughout the course of the pregnancy except that she had continued to have moderate gastrointestinal upsets and some pain and discomfort throughout the abdomen. On or about July 15, she had developed what she thought was labor, having fairly regular pains which became progressively more severe, and when they were eight minutes apart she entered the same hospital in which she had been operated upon in January of 1947. There an injection of Demerol was given and the labor ceased. Since that time she had not felt the baby move and two other doctors had examined her and neither could hear a fetal heartbeat. She had general malaise and more or less constant abdominal pain. It was becoming more difficult for her to eat and retain any nourishment and she was losing weight and strength. Examination at this time revealed the fundus of the uterus to be 23 cm. above the symphysis pubis which would indicate a 29 weeks' gestation. X-ray examination disclosed a fetus estimated at the twenty-eighth week lying generally in a transverse position with a very acute angulation of the vertebral column and the skull bones overlapping as much as 3 cm.

She was admitted to the Decatur General Hospital on Aug. 23, 1947. In spite of the fact that the cervix was hard and fibrotic and not dilated, a medical induction was attempted without success. Following a telephone conversation with the consultant at the medical center previously referred to, she was given twenty thousand units of estradiol, three times daily for three days, and a second medical induction attempted, again without success. During the first week in the hospital, she was given large doses of vitamins, liver extract, iron, high-protein diet, and was thoroughly hydrated. However, the abdominal pain continued to get progressively worse. The patient appeared to be toxic and was unable to take sufficient nourishment by mouth. She was constantly becoming weaker, in spite of blood transfusions and a normal fluid and electrolyte balance. After several consultations it was decided that an abdominal hysterotomy was indicated. On September 1, the thirty-seventh week after the last menses, the patient was taken to surgery and open drop ether was begun. Her blood pressure at the time was 92/68. Almost immediately

after the beginning of the induction, she went into a severe shocklike condition with the heart rate 176 per minute and the blood pressure unobtainable. Oxygen was administered and 500 c.c. of plasma started immediately. Within a period of about thirty minutes she apparently had recovered from her shock and a light surgical anesthesia was given with open drop ether. A lower midline incision was made opening into the peritoneal cavity. The baby was found lying loose in the abdominal cavity outside the membranes, covered with a thick plastic exudate and was adherent to the anterior abdominal wall, to the undersurface of the liver, the transverse colon, the ileum, and to the thickened membranes. The membranes were distended, making a mass approximately the size of a 28 weeks' gestation. The dead infant was easily separated from its adhesions to the surrounding structures. The cord was cut and the fetus removed. When gentle traction was made on the umbilical cord an old tear in the membranes on the right side was reopened and a large amount of fluid escaped. These membranes appeared grossly much thicker than is normaily seen and on the inside of the sac were two hard masses approximately 8 and 10 cm. in diameter. While the area was being inspected, approximately 200 c.c. of old black blood welled up into the wound from the region of the cul-de-sac, followed by a free flow of bright red blood. Old organized blood clots were removed from the right side of the pelvis to the point where the ovarian pedicle could be clamped and ligated. The two hard masses inside the membranes which were thought to be organized placental tissue and organized blood clot were removed. As much of the membranes was trimmed off as possible and the capillary and venous bleeding was controlled with hot abdominal packs. After satisfactory hemostasis a Penrose drain was placed into the cul-de-sac and the abdomen was closed in layers. During the day the patient received 1,000 c.c. of plasma and 900 c.c. of whole blood. For the next two days she was in a fair condition with a gradual improvement of her shocklike state and the pulse returned to around 100 to 110 per minute, which was slower than it had been prior to operation. She received adequate replacement for electrolyte loss and adequate whole blood and plasma. In addition she was given adrenal cortex extract for possible adrenal failure. She was taking water and clear fluids by mouth and appeared fairly comfortable. On September 3 she developed a mild abdominal distention which became moderately severe on September 4. Her blood pressure at this time was around 106/80, compared with a systolic of 80 to 90 prior to operation. From this time on the patient showed a decline in her general condition. On September 5 she developed a tremendous distention, her temperature was above 104° F., pulse rate increased from 140 to above 200 per minute, with a falling blood pressure. At consultation it was decided that an ileostomy should be performed immediately inasmuch as her condition had become desperate. Under local anesthesia a muscle-splitting incision was made in the right flank and a large catheter was placed into what was thought to be a loop of ileum which was under extreme distention. Six thousand c.c. of fluid were removed with a large amount of gas. A definite odor of putrefaction was present. The patient immediately improved upon release of the abdominal distention; however, her condition was still critical. She had received 50,000 units of penicillin every three hours following the first operation. Within a few hours after the ileostomy was performed her temperature was 108° F. by rectum and she was in a coma from which she did not recover. On September 6 she showed evidence of carpopedal spasm, muscular twitching, and some tonic spasm of the masseter muscles. Apparently her electrolyte balance had been disturbed by the loss of a large quantity of fluid, and calcium gluconate was added to the Ringer's solution and glucose which were being administered. Following the work of Darrow and others, she was also given potassium chloride intravenously. Following the administration of the potassium and calcium, she appeared considerably improved, her respiration became more nearly normal, the carpopedal spasm and muscular twitching improved, and the depth of the coma seemed to be diminished. The abdomen remained flat and her color improved to the point where the oxygen tent was discontinued. On the morning of September 7, the patient went into a sudden severe, clonic convulsive seizure and died.

Postmortem examination revealed that the area which had been occupied by the dead infant was completely sealed over by a thick plastic exudate which separated the abdominal viscera from the anterior abdominal wall. The rubber catheter was found extending into the peritoneal cavity which had become so markedly distended. The cavity contained approximately 2,000 c.c. of old amniotic fluid, meconium, and old blood. The stomach and the intestinal tract contained a small amount of fluid and gas. Both tubes and ovaries appeared to be grossly normal.

The cause of death in this patient was never adequately explained. She was not taking intravenous fluid or medication at the time nor had she had any calcium or potassium salts in a period of several hours at the time of her death. The manner of her death, in a clonic convulsive seizure, accompanied by the preceding tonic spasm of the masseter muscles would indicate the possibility of tetanus infection. Her nonprotein nitrogen 48 hours prior to death was 102 mg. per cent. Approximately 12 hours prior to her death, the red count was 3.5 million, hemoglobin 11 Gm., white blood count 11,600, with a normal differential count. The urinalysis was normal with the exception of an occasional large hyaline cast. It is regrettable that permission for a complete postmortem could not be obtained. All indications point to a primary abdominal pregnancy, followed by escape of the fetus from the membranes. The rent in the membranes was sealed over, permitting distention with fluid to the size of a seven months' pregnancy. Severe toxemia developed, followed by adrenal failure. Tetanus is considered the immediate cause of death.

CASE 2.—(28601-28656) A Negro woman, aged 23 years, A. W., gave a family history and past history which were entirely irrelevant. Menstruation began at the age of 11 years with a normal interval, duration, and quantity of flow. In 1945, she developed pain in the right tubovarian region approximately four days prior to the onset of each menstrual period. This would subside during the first day of flow. She married in September, 1947, and had noticed dyspareunia four or five days prior to each period. She did not have any chills or fever or other evidence of pelvic inflammatory disease.

Her last normal period was February 28, but bleeding started again March 27, 1949. At this time she spotted for a period of two days and this was followed by a normal flow of two days' duration. Following this, she continued spotting every day until May 4, at which time she reported to a doctor in a neighboring city who did not think she was pregnant but found a very badly infected cervix. He did a biopsy of the cervix and sent the tissue in for pathologic study. Following the biopsy, he performed a cauterization which stopped the bleeding. She stated that early in April she developed a pain which was generalized throughout the lower abdomen and pelvis and was continuous in nature with occasional acute exacerbations. During April, she developed indigestion, belching, and nausea but no vomiting. During the latter part of April and May the pain became more or less localized in the right lower quadrant of the abdomen and was more severe at the tubovarian reflex point and along the crest of the right ilium and in the right inguinal region.

One week after the biopsy and cauterization of the cervix, which were done on May 4, the patient started running a fever and having chills. At this time a diagnosis of pelvic peritonitis was made. She was hospitalized and started on a course of penicillin. The chills and fever subsided during a period of a week and she was discharged as improved. About two weeks later, on coming to Decatur, she had another episode of chills and fever and was admitted to a local hospital where she was again given penicillin and a blood transfusion. The vaginal bleeding started again on August 15 and she had some spotting every day from that time on. At times the bleeding would be quite heavy. On the passage of a heavy flow of blood, the severe pain in the pelvis would be relieved.

The patient was first seen by me on Sept. 23, 1949, at which time the uterus was noted as being the size of a 26 weeks' gestation. The cervix was about three times normal size, very markedly congested, and was displaced anteriorly toward the symphysis pubis.

An indefinite cystic mass was found posterior to the cervix in the cul-de-sac. The cervix showed a very extensive erosion with an area of granulation tissue on the posterior lip which was bleeding more or less continuously. Inasmuch as this had the gross characteristics of a possible malignancy, multiple punch biopsies were obtained for a microscopic study. The bleeding was controlled with coagulation current. The biopsy failed to show any evidence of cancer. At the time of this examination the main body of the uterus appeared to be displaced to the right side of the abdomen with the baby located in the left portion of the fundus of the uterus, lying over the maternal spinal column. X-ray examination at this time showed no evidence of placenta previa and the possibility of a bicornate uterus was considered. On the night of September 24, the patient developed nausea, vomiting, and increased pain in the lower abdomen along with a tetanic contraction of the uterus. On examination on September 25, the fetal heart could not be heard and the patient was given 100 mg. of Demerol and admitted to the hospital. She received relief of the pain from the Demerol. The laboratory reports were within normal limits except for a moderate anemia, her red count being 3.7 million with 9.8 Gm. hemoglobin. Serologic examination was negative. After the uterus relaxed, the fetal heart was again heard in the left side of the uterus at a rate of 176 per minute, regular and with a fair volume. Consultants were called in and the patient was further examined and the possibility of several different pathological conditions were discussed, but no diagnosis was made. It was the consensus that the patient should be carried on for a while longer to await viability of the child before delivery was attempted. After receiving blood transfusions, she was discharged from the hospital on Sept. 27, 1949, on a high-protein diet with a vitamin and iron supplement.

On October 2, she developed a chill followed by high fever and increasing lower abdominal pain. Her local Negro physician had been administering penicillin, 400,000 units daily. This was increased to 400,000 units twice daily and she was given one of the sulfonamides. The chills and fever became more severe and she became quite toxic with a temperature running between 105 and 106° F. some three or four times daily. On Oct. 6, 1949, her local doctor advised me of her condition and the patient was readmitted to the hospital with a tentative diagnosis of tubovarian abscess, right, with a dead fetus.

On admission she showed a marked emaciation with loss of electrolytes and fluids. She was acutely ill and very toxic with a temperature of 104° F., pulse 130, respiration 32, and blood pressure of 110/60. The pathological findings were related primarily to the reproductive system. The abdomen was filled with a rounded oval mass which was located more on the right than on the left side, extending from the pelvis up beyond the rib margin on the right and approximately one inch above the umbilicus as it crossed the midline. The fetus was palpable in the left portion of this mass over the maternal vertebral column. The uterus appeared to be in a moderate tetanic contraction and the parts were palpated with some difficulty. The fetal head could not be forced down into the pelvis. Extreme tenderness was elicited along the crest of the right ilium and above the inguinal ligament. This was accompanied by pain radiating down the anterior portion of the right thigh. No bleeding was present at the time. The cervix was long, firm, and displaced anteriorly almost against the symphysis. An indefinite mass was palpated posterior to the fundus and the cervix, and no fluctuation could be made out in the cul-de-sac. X-ray examination showed the fetus situated over the maternal spinal column with the vertex presenting but not engaged. The skull bones were overlapping. The patient was estimated to have a 32 weeks' gestation, complicated by a right tubovarian abscess which resulted from an old pelvic inflammatory disease. Because of the extreme weakness, toxicity, and obviously serious illness of the patient, she was given large amounts of intravenous fluids, including 1,700 c.c. of whole blood during the next 48 hour period. She was started on large doses of penicillin and streptomycin on admission on October 6. By October 9 she was showing some evidence of improvement and her red count had been brought up to 4,150,000, with hemoglobin of 11.35 Gm. By October 11 she had started taking small amounts of nourishment by mouth and was less toxic and felt considerably better. By October 12 she had re-

ceived 2,700 c.c. of whole blood. After repeated consultations it was decided that she should have a drainage of the abscess at its point of greatest fluctuation. On October 13 which was the thirty-second week of gestation, the patient was prepared for surgery and under gas, oxygen, and ether an incision was made in the right flank 2.5 cm. superior to the crest of the ilium between the anterior and the midaxillary lines with the idea of inserting a drainage tube into the abscess and allowing her to make further improvement before an attempt at delivery. When a short incision into the cystic mass was made a very brisk flow of bright red blood appeared and the incision had to be quickly extended in order to control the hemorrhage. At this time one foot of a badly macerated infant was seen. This was seized, the infant extracted, and pressure applied to control the hemorrhage. An extremely foul odor of putrefaction was present. On inspection it was found that most of the tissue on the right side of the infant's abdomen and all the soft tissue on the posterior aspect of the chest had been completely destroyed by putrefaction, leaving exposed the vertebral column and the ribs. The lungs apparently had been completely destroyed. The placenta appeared to be very necrotic and was loose in its major portion in a mass that presented at the upper edge of the incision. As much of it as possible was trimmed off from its attachments in the abdomen. Because the patient had gone into extreme shock it was necessary to close the abdomen without satisfactory exploration. However, the placenta had been attached in the right upper quadrant. The bleeding was brought under control with large hot saline packs but when these were removed after a period of ten minutes of continuous pressure, the bleeding recurred to an excessive degree. Consequently it was elected to replace the packs and close the abdomen leaving three packs inside the peritoneal cavity. The patient received both plasma and whole blood during the operative procedure. By the time the abdomen was closed her blood pressure had returned to 100/52 and the pulse rate was around 140. She made a satisfactory improvement and on October 15, 48 hours after the operative procedure, the abdominal packs were removed without the wound having to be reopened. A small amount of old blood was present but no fresh bleeding was encountered. Two large Penrose drains were inserted into the bottom of the abdominal wound. The patient continued to show improvement and had a very copious drainage of foul-smelling old blood and necrotic tissue. She had a small amount of abdominal distention postoperatively and received multiple small transfusions throughout her postoperative course. By October 25, practically all the placenta had been passed and the wound was granulating in. She was symptom free, eating well, and ambulatory. On November 5 she was discharged from the hospital with a red count of 3.8 million and a hemoglobin of 10.6 Gm.

The patient was followed at the clinic and apparently made a normal recovery. On Feb. 16, 1950, a Rubin test showed a partial obstruction of the left tube with the right tube completely obstructed at the cornual portion. Hysterosalpingography was performed for verification. In June the patient was found to have a left ovarian cyst approximately 6 cm. in diameter. Careful follow-up showed a gradual decrease in the size of this cyst to normal. On Sept. 25, 1950, forty-nine weeks after her primary operation, the patient returned to the clinic complaining of severe dyspareunia, dysmenorrhea, and a constant soreness and pain in the pelvis accompanied by frequency and urgency. Laboratory reports were within normal limits except for an elevation of the red cell sedimentation rate which was 56 mm. on a Wintrobe tube. Examination disclosed the pelvis filled with a left ovarian cyst. This was extremely tender on palpation and was making pressure on the bladder and displaced the uterus to the right side of the pelvis. The patient was readmitted to the hospital and on September 25 the abdomen was opened and an extensive inflammatory condition of the entire pelvis was encountered. A mass of chronic inflammatory tissue replaced the entire right adnexa and the cornual portion of the right tube was the only portion which could be recognized. This showed a definite salpingitis nodosa. When the right adnexal mass was dissected out, an abscess was opened and approximately 30 c.c. of thick yellow material were evacuated. The uterus was found pushed down deep into the

cul-de-sac and intimately adherent to the posterior wall of the cul-de-sac. The left tube and ovary were incorporated into an old chronic inflammatory mass of adhesions and here again the ovarian tissue could not be grossly recognized. The fimbriated end of the tube was lost in the inflammatory mass and a moderately severe hydrosalpinx was present. At this time a bilateral salpingo-oophorectomy, lysis of adhesions, and suspension of the uterus were performed along with an incidental appendectomy. The patient made a smooth convalescence and was discharged from the hospital on October 3 with the wound well healed.

On return visits to the clinic, it was found that the patient had resumed her normal menstrual function. Her periods were at 28 day intervals, 4 days in duration, with no pain or cramps. Shortly after the laparotomy in September of 1950, she developed an inflammatory type cyst in the left side of the pelvis which gradually subsided over a period of four months. In December of 1951, the patient reported back to the clinic that she had developed excessive "gas on the stomach" with belching and bloating, and had noticed that the lower abdomen was again enlarging. She stated it had been impossible to obtain a bowel movement without the use of a laxative during the past few weeks. She also had frequency but no burning and mild dyspareunia was present. She had gained considerable weight since her operation, in 1950, and now appeared to be quite healthy and well. Examination at this time revealed a large cystic mass which extended up to above the level of the umbilicus and was tender on palpation. The cervix was found displaced high behind the symphysis pubis and far to the right of the midline near the right wall of the pelvis. The uterus was apparently normal in size and consistency. The cul-de-sac contained a cystic mass which was apparently continuous with the abdominal mass. On Dec. 12, 1951, 26 months after the original operation, an exploratory laparotomy was performed. A large multilocular, blue-colored, thin-walled cyst apparently arose from a remnant of left ovarian tissue. This completely filled the cul-de-sac and extended over the crest of the ilium bilaterally and filled the entire lower abdomen. The cyst extended between the leaves of the broad ligament on the left side and was very densely adherent to the posterior aspect of the uterus and the right and left pelvic walls and the rectum posteriorly. By a combination of sharp and blunt dissection, the cyst was dissected out. Two thousand six hundred c.c. of greenish thin fluid were aspirated from the cyst cavity. The cyst wall could not be dissected from the rectum and the posterior wall of the cul-de-sac. A complete hysterectomy was performed. The pathologist did not find any evidence of malignant disease in the tissue. Recovery was uneventful.

CASE 3.—(28726) D. J., a Negro woman, aged 35 years, was admitted to the hospital Oct. 19, 1949, as a para 0, gravida i, at 35 weeks' gestation, with a transverse position. Her family history and past history were entirely irrelevant. The patient had had no serious illnesses, injuries, or operations. Her menstrual periods had been irregular with an interval of four to six weeks, and a duration of four days and normal quantity of flow. She had always had a mild midline suprapubic cramp the first day of the flow. She married in 1939, and contraceptives were never used. The last menstrual period was Feb. 17, 1949. Early in March she developed a mild soreness in the right side of the abdomen and went to see her doctor who gave her several injections of penicillin over a period of three weeks. The pain at no time was severe in nature nor was it accompanied by any symptoms referable to the urinary tract or rectum. There was at no time any pallor, extreme weakness, or fainting episode. Her digestion remained perfectly normal and aside from a very mild discomfort in the lower abdomen her general physical condition was excellent. In July she had a mild colicky pain in the right lower quadrant of the abdomen and her doctor at that time told her she had a tumor in the pelvis but that surgery was not recommended at that time. Shortly after this she began feeling fetal movements and felt reasonably sure she was pregnant. One week prior to admission to the hospital, the patient started having irregular labor pains and her physician prescribed some 50 mg. Demerol tablets which she took at fairly frequent intervals but without relief of pain. The night of October 17, the patient was unable to sleep because of the severity of the pains and she was referred to me for cesarean section.

On admission she was found to be a well-developed and well-nourished Negro woman of about 35 who was having painful uterine contractions. Her temperature, pulse, and respiration were normal, the blood pressure was 110/80. Examination of the abdomen showed what appeared to be a pregnant uterus approximately at term with the long axis of the uterus in the transverse position. The baby was palpated in a transverse position with the head on the left side of the abdomen. The Hillis maneuver was unsuccessful. The uterine wall apparently was of normal consistency and the uterine souffle was more pronounced on the right side of the abdomen. Inasmuch as a section was contemplated, vaginal or rectal examinations were omitted. The patient was prepared for surgery, adequate blood supplies were obtained, and the patient was taken to the operating room on October 19. Under cyclopropane the abdomen was opened through a lower midline incision. The anterior surface of the uterus appeared normal for a full-term pregnant uterus. The infant's head was easily palpated through the anterior uterine wall. The incision was made as for a low classical section and it was found that the uterine wall was extremely thick. However, the baby's head could still be palpated immediately below the incision so it was carried still deeper until the membranes were reached and the baby was quickly delivered through the uterine wound. The hemorrhage was extensive at this time and, as the baby was being delivered, 1 c.c. of Pitocin was injected into the uterine wall. The uterus contracted very promptly and the hemorrhage was controlled. The baby was about the proper size for an 8 months' gestation and resuscitation was difficult. The baby had a meningocele, cleft palate, hare lip, and several other congenital anomalies, and lived for a period of approximately 12 hours after delivery.

Inspection of the uterus was made and it was found that the incision had gone entirely through both the anterior and the posterior walls of the lower uterine segment into an abdominal pregnancy situated behind the uterus. The fundus of the uterus was found to be adherent to a loop of transverse colon and the placenta was found attached to the posterior wall of the cul-de-sac across its floor and along the posterior aspect of the uterus. It was also attached to the mesocolon and to the colon itself and ileum. Multiple large blood vessels, several of which were 1 cm. in diameter, extended from the intestinal tract to the placenta. The membranes were quite thick and apparently had filled most of the abdominal cavity posterior to the uterus extending down into the cul-de-sac and completely enveloping both tubes and ovaries which could not be recognized until the membranes were trimmed away. The umbilical cord was approximately 20 cm. in length and 1 cm. in diameter. Because of the large blood vessels entering the placenta from the mesocolon, colon, and ileum, no attempt was made to remove the placenta. As much as possible of the membranes was removed, the anterior and posterior uterine walls were sutured in the usual manner, and the wound was closed without drainage. The patient was in moderately severe shock for a period of two hours postoperatively and then made a satisfactory recovery. An adynamic ileus was present for approximately 48 hours. During the first five postoperative days a total of 4,250 c.c. of whole blood was given. On October 27 the patient developed a thrombophlebitis of the left great saphenous vein which gradually subsided. Examination on October 28 showed the abdomen to contain a mass which was approximately the size of a 7 months' gestation. This mass gradually decreased in size and the patient was discharged from the hospital on November 13 with the wound well healed and apparently free of infection.

Nine weeks after the primary operation the patient was readmitted to the hospital on Dec. 24, 1949, with a history, physical findings, and x-ray evidence of a high intestinal obstruction of 48 hours' duration. She was unable to retain even small quantities of liquids and complained of localized pain approximately 5 cm. to the left and 5 cm. above the umbilicus. During the next five days, the abdominal distention was entirely relieved by suction and the electrolyte and fluid balance was restored to a normal level. On December 29, the abdomen was opened and found to contain adhesions uniting practically all loops of small and large gut. These adhesions were thin and delicate and the entire proximal third of the ileum was distended to approximately 4 cm. in diameter with the

distal two-thirds being flat. A complete obstruction due to a band of adhesions was found on the left side of the upper abdomen at the point indicated by the patient's pain. The adhesions were released. Examination of the pelvis showed the uterus displaced far to the right side of the pelvis, the right tube and ovary were imbedded in a mass of old decidual tissue with moderately firm adhesions surrounding and completely filling the cul-de-sac. A large abscess with thick yellow material was located behind the uterus and filling the space from the left lateral wall of the pelvis over to the right of the midline in the cul-de-sac. The pus was aspirated. In the attempt to remove the remaining decidual tissue and placenta from the cul-de-sac an extensive hemorrhage developed which required total hysterectomy for control. Smears and cultures from the pus removed in this abscess were negative for bacteria. The patient made an uneventful recovery and has remained in good health.

CASE 4.—(30635) Mrs. R. B., white, aged 32 years, was admitted to the hospital Nov. 1, 1950, as a patient of Dr. G. H. Nungester. Her past history was of interest in that she had several spontaneous abortions and her three living children all weighed between 3 and 4 pounds at birth. She had a spotting of blood or frank bleeding from the uterus at intervals throughout each of her pregnancies. The last normal period occurred on April 24. On May 22, 1950, because of pain, cramping, and bleeding, she was examined and thought to be pregnant. The adnexa were normal to palpation. She was put on bed rest and conservative treatment for threatened abortion. She ate fairly well and gained weight but complained more or less continuously of epigastric pain and vomited almost every day. The pain was definitely more severe if she was in an upright position and would be somewhat relieved by lying down. The uterus continued to enlarge but was asymmetrical with most of the enlargement being in the right side of the abdomen. The baby started moving early in July, which indicated fecundation after her period of March 26. The movements caused more abdominal pain than is usually expected. On each examination a definite firm mass was noted on the right side of the abdomen and the baby could not be moved from side to side as easily as one normally expects. The tubes and ovaries were not palpably enlarged. Early in October, the patient developed a rapid gain in weight, pitting edema, and four plus albuminuria. On bed rest and a low-salt, high-protein diet she lost 18 pounds in two weeks and her blood pressure was still within normal limits. She still showed a two plus albuminuria and a few red cells at this time. On October 31, her systolic pressure had changed from 130 on the last visit to 150 with a corresponding increase in diastolic pressure. Consequently she was admitted to the hospital on November 1 for further treatment. On admission she showed pitting edema of the lower extremities and blood pressure of 170/80 and a mass in the abdomen about the size of a 37 weeks' gestation. This rather firm globular mass was almost entirely on the right side of the abdomen and appeared not freely movable. The fetal parts could not be easily identified. The heart tones were clear and regular high in the upper right quadrant of the abdomen. X-ray examination showed that a fetal skull overlay the maternal spinal column with the trunk and the lower extremities of the fetus extending up behind the liver shadow. A pocket of gas in the ileum was found very close to the shadow of the fetal skull so it was felt that pregnancy was extrauterine. The patient showed a hemoglobin of 9.5 Gm., with 3.5 million red cells. She was type O, Rh negative. Tests for blocking antibody were not obtained. The urine showed a four plus albuminuria with a few hyaline casts and six to eight white blood cells per high-power field. On admission, the patient received 2 pints of whole blood and under sedation her blood pressure fell to within normal limits. On November 2, the abdomen was opened under spinal anesthesia and the fetal head was seen immediately beneath a thin layer of membranes just inside the peritoneal cavity. A poorly developed monstrosity about the size of a 7 months' fetus was delivered. The heart continued to beat for a period of approximately four to five minutes but the baby was not resuscitated. Multiple congenital malformations were incompatible with life. The umbilical cord was ligated as close as possible to the placenta. Any attempt at removing the membranes or placenta was followed by a very profuse hemorrhage which was controlled with abdominal packs.

Because of the extreme vascularity, it was inadvisable to attempt removal of the secundines and each time pressure with the abdominal packs was released hemorrhage recurred. Consequently three abdominal packs were left in the wound and the abdomen was closed, the attached tapes extending out through the central portion of the operative wound. The patient progressed well and 72 hours after the primary laparotomy the abdominal packs were teased through the operative wound under gas analgesia. No hemorrhage recurred following the removal of the packs. The patient was discharged from the hospital on Nov. 15, 1950, with a moderate serosanguineous drainage from a sinus in the central portion of the operative wound. There was no odor present and no evidence of infection.

The patient remained afebrile and felt fairly well up until the middle of December. At that time drainage from the sinus in the operative wound became much more profuse and sanguineous in nature, and a palpable oval mass in the left lower quadrant of the abdomen which had been present since the patient was discharged from the hospital was noted to have increased in size considerably in a period of one week. During this period of time she had considerable weight loss and pain in the left side of the abdomen and was developing a progressively severe secondary anemia. She was readmitted to the hospital on Dec. 26, 1950, and after restoration of blood volume and fluid balance the abdomen was reopened. A rounded smooth mass composed of intact membranes containing amniotic fluid extended up above the level of the umbilicus on the left side of the abdomen and while the omentum was adherent in several places, there were no adhesions to the intestinal tract at any point. By a combination of sharp and blunt dissection the mass was freed from the surrounding structures down to the left tube and ovary and posterior surface of the broad ligament. The tube and ovary could not be separated from the mass and had to be removed. A moderate capillary oozing was controlled with hot wet packs. After thorough hemostasis the wound was closed in the usual manner with no drainage. The postoperative course was uneventful with the exception of a small area of atelectasis in the right lower lobe which developed 24 hours postoperatively. She was discharged from the hospital on Jan. 18, 1951, apparently in good condition. She got along very nicely for several months and then moved out of the state and has not been contacted since that time. The case is assumed to be a primary abdominal pregnancy inasmuch as there is no history to indicate a tubal abortion, neither tube was palpably enlarged at the multiple examinations throughout her early pregnancy and both tubes were intact at the time of the secondary operation.

CASE 5.—(32476) A Negro woman, aged 25 years, was also a private patient of Dr. G. H. Nungester. This patient was admitted to the hospital on Sept. 19, 1951. She had a normal pregnancy and labor eight years previously and subsequently had been treated several times with penicillin for pelvic infection. Her last menstrual period occurred on June 17, 1951. On August 22, she started a painless bleeding which persisted for a period of five days before moderate pelvic cramping pain occurred. She continued to have pain in the right lower quadrant of the abdomen and the sacral region and on the day of admission a pelvic mass was palpated bulging into the cul-de-sac. The entire lower abdomen was slightly enlarged with extreme tenderness in the suprapubic region and a slightly fluctuant mass was palpated in the right lower quadrant. The pelvic mass was approximately the size of a 14 or 15 weeks' gestation. She had 2.7 million red cells with 4.95 Gm. hemoglobin; serologic examination was negative. She was placed on penicillin and streptomycin therapy, given multiple blood transfusions, her electrolyte and fluid balance was corrected, and on September 28 the abdomen was opened. The oval mass proved to be membranous, contained amniotic fluid and a living fetus which was estimated to be of 14 or 15 weeks' gestation. The placenta was attached to the lateral pelvic wall and broad ligament. Hemorrhage was moderately severe but clamps placed on the cornual portion of the tube and the right ovarian pedicle controlled the hemorrhage satisfactorily. The right tube and ovary were removed along with the placenta and membranes. Hemorrhage was controlled with hot wet packs and the abdomen was closed in the usual manner without drainage. Microscopic study of the tube showed fine villuslike

processes. This definitely is a case of secondary abdominal pregnancy which aborted from the right tube. The patient made an uneventful recovery and was discharged from the hospital on Oct. 18, 1951, apparently in good condition.

Comment

It is very difficult to be positive as to which cases of abdominal pregnancy are primary and which are secondary. However, it is felt that Case 1 is primary and probably Cases 3 and 4 should be considered primary. Cases 2 and 5 are undoubtedly secondary. The escape of the fetus from the amniotic sac as given in Case 1, followed by a resealing and refilling of the amniotic sac with fluid, is considered an extremely rare condition. Case 3 is also of interest in that the body of the uterus extended up into the upper abdomen and was thinned out to the extent that the infant's head was palpated through both walls of the lower uterine segment and the extrauterine nature of the pregnancy was not discovered until after the baby was delivered. The extremely toxic condition of the mother in both Cases 1 and 2 is of interest.

My experience with these five cases and with the two reported by Burleson and Bragg does not permit an authoritative opinion as to treatment of these conditions. However, it is felt that if the condition is discovered in early pregnancy it is safer to terminate the pregnancy immediately by laparotomy. If the infant is apparently normal and almost viable, a reasonable delay may be made until approximately the thirty-sixth week of gestation. The treatment of the placenta is a controversial subject. My experience indicates that if the placenta can be removed easily, as it frequently may be if the baby has been dead for several days, then by all means as much of the secundines as possible should be removed. In these cases, while the hemorrhage may be considerable, it is generally controlled with pressure with hot gauze sponges. If the baby is alive at the time of the operation and the placenta implanted in the pelvis, there again the possibility of extreme hemorrhage is encountered, and a complete hysterectomy may be required to control the hemorrhage. If the major portion of the blood supply to the placenta arises from the liver, colon, ileum, or other structures which could not be easily removed at that time, then it is best to leave the placenta undisturbed, trimming off only avascular membranes. The majority of these patients will go into severe shock during the operative procedure, and it is most important that adequate hydration and blood volume be restored prior to operation and that adequate whole blood be available during the time of the surgery. The use of antibiotics and chemotherapy will permit many of these patients to live who might otherwise succumb to infection.

I am unable to explain the high incidence of ectopic gestation seen in the Decatur General Hospital. It is felt, however, that cases of ectopic gestation will be seen more and more frequently as time goes on, especially among the lower income group of patients. It is recognized by all that any disease process which interferes with the passage of a fertilized ovum through the Fallopian tube may result in an ectopic gestation. Chemotherapeutic agents and antibiotics have now become commonplace articles which in many drug stores are sold over the counter to any person who requests them, and in many places they are being prescribed by pharmacists in small and inadequate doses. Many patients who develop a salpingitis, either specific or nonspecific, will attempt self-medication and consequently take just enough of the agent to aid in getting over the acute attack and possibly prevent complete occlusion of the tube. However, the tube will be left in a sufficiently diseased condition that the sperm can pass through without difficulty and fertilize the ovum but the fertilized egg in turn cannot return to an intrauterine sanctuary. Another etiological factor seen with increasing frequency is endometriosis. Several

patients operated on by the author in the last five years have shown unmistakable evidence of this condition.

Summary

Five cases of abdominal pregnancy are presented with laparotomy occurring in the thirty-seventh, thirty-second, thirty-fifth, thirty-second, and fourteenth week of gestation, respectively. Two of the babies were dead at the time of delivery. Three were alive at delivery but did not survive. One mother died probably from tetanus on the seventh postoperative day. All of the other mothers were living and in good health at the time this paper was prepared.

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CARCINOMA OF THE UTERINE CORPUS

A Study of 184 Cases Seen at the Rhode Island Hospital, 1922 to 1945*

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THIS study was undertaken primarily with the idea that, by a careful investigation of all the factors involved in the life history, symptomatology, diagnosis, and treatment of carcinoma of the uterine corpus as seen at this clinic, a better understanding of the disease might be achieved. Also, conclusions might be drawn leading to improved methods of treatment and consequently better results as shown by patient survival.

Material Studied

The general factors presented here are based on statistics compiled from 184 consecutive cases of carcinoma of the uterine corpus seen in the Gynecological Tumor Clinic of the Rhode Island Hospital during the years 1922 to 1945. The five-year salvage rates presented here are based on 126 consecutive patients treated at the Gynecological Tumor Clinic during the years 1936 to 1945.

General Factors

Frequency.—Next to cancer of the uterine cervix, cancer of the uterine corpus is the most common neoplasm of the female reproductive organs. Although it has been pointed out by Meigs[1] and others that the ratio of occurrence of carcinoma of the cervix and carcinoma of the corpus is fairly constant, our recent experience has indicated a relative increase in the incidence of carcinoma of the corpus. Whereas in the years between 1933 and 1943 at our hospital we saw four cervix cancers to one corpus cancer, during the past five years we have seen only three cervix cancers to every corpus cancer.

Table I demonstrates our over-all experience with the two diseases between the years 1933 and 1950, during which time carcinoma of the corpus represented 26 per cent of the combined total.

Marital Status.—One hundred fifty-eight of the 184 patients, or 85.9 per cent, were married. This figure is comparable to that of Palmer[2] of Buffalo, who reported that 89 per cent of his patients were married. Other series give the following figures for the percentage of married women: Corscaden,[3] 76 per cent married; Norris and Vogt,[4] 74 per cent; Healy and Brown,[5] 84 per cent married; Speert,[6] 82 per cent. On the average, 80 per cent of women with carcinoma of the corpus are married. In our recent study of carcinoma of the uterine cervix[7] we found that 98 per cent of the group were married. Therefore, there seems to be a significant difference between the two diseases with respect to the marital status.

Parity.—Thirty-three per cent of our group as a whole had no children. Corscaden[3] found 38.6 per cent childless women in his study of corpus cancer;

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Hertig,[8] 39 per cent. Twenty-three per cent of the married women in our group were childless. Palmer[2] states that 19 per cent of the married women in his series of corpus carcinoma were childless. In contrast, only 12 per cent of our patients with cervix cancer were childless.

TABLE I. RATIO OF CANCER OF CERVIX TO CANCER OF CORPUS AT RHODE ISLAND HOSPITAL, 1933-1950

YEAR	NO. OF CASES		PERCENTAGE OF CASES OF CANCER OF CERVIX	PERCENTAGE OF CASES OF CANCER OF CORPUS
	CORPUS	CERVIX		
1933	11	54	83	17
1934	11	38	77	23
1935	6	31	84	16
1936	5	35	88	12
1937	9	38	81	19
1938	8	40	83	17
1939	14	35	71	29
1940	10	34	77	23
1941	13	33	72	28
1942	16	52	77	23
1943	14	42	75	25
1944	14	33	70	30
1945	19	45	70	30
1946	18	46	72	28
1947	20	44	68	32
1948	25	35	58	42
1949	21	45	68	32
1950	16	32	67	33
Totals	250	712	74	26

The significance of this relative increase in childlessness observed in corpus cancer is not as yet understood. Hertig[8] observed that parturition appeared to defer the establishment of neoplastic endometrium and stated that, at present, it was uncertain whether this was due to the maintenance of normal endometrial physiology due to the hormonal changes of pregnancy or due to the complete endometrial shedding that occurs with delivery.

Economic Status.—Fifty-seven per cent of our group were private patients. This is in contrast to our patients with cancer of the cervix, the majority of whom were ward patients. Corscaden[3] has also found this true in his series: 47 per cent of his corpus cancer patients were private, compared to only 24 per cent of his cervix cancer patients. It has been theorized that economic security leads to overindulgence in food with resultant obesity, hypertension, and diabetes—all allegedly associated with carcinoma of the corpus. Nevertheless, the full meaning of this observed increase in economic security of patients with corpus cancer over those with cervix cancer remains obscure.

Age.—The average age of our patients with corpus cancer is 61 years as compared to an average age of 51.2 years with cervix cancer. Other authors report similar figures: Hertig,[8] 57.2 years; Hundley,[9] 55.9 years; and Peightal,[10] 56 years. It is interesting to note that 87 per cent of our cases occur after the age of 50. The range of ages in our group was from 40 to 81 years.

Religion.—Fifty-eight per cent of our group were Protestant, 35 per cent Catholic, 2 per cent Jewish, and 5 per cent belonged to other religious groups. According to population statistics for Rhode Island, it would seem that in this community the disease is relatively increased in Protestants and relatively decreased in Catholics and Jews.

Menopause.—Eighty-five per cent of the patients in our series were postmenopausal. Palmer[2] reports that 79 per cent of his cases of corpus cancer

occur after the menopause. The average age at menopause in our cases was 49.6 years. This concurs with Palmer,[2] 49; Peightal,[10] 49; and Hertig,[8] 47.

Although Randall[11] states that only 8 per cent of the women in the general population menstruate to the age of 50, and Crossen and Hobbs[12] gave this figure as 15 per cent, 51 per cent of our patients menstruated beyond the age of 50. It would seem, therefore, that late menopause with a persistence of estrogen stimulation is a significant factor in the development of cancer of the corpus. However, according to Corscaden,[3] many gynecologists feel that what is termed a delayed menopause may actually be a symptom of a developing corpus cancer.

TABLE II. A STUDY OF 184 CASES OF CARCINOMA OF THE URINE CORPUS SEEN AT RHODE ISLAND HOSPITAL BETWEEN THE YEARS 1922 AND 1945

1. Marital status	85.9% married; of these, 23% childless	
2. Parity	33.3% childless	
3. Economic status	57% private patients	
4. Age	Range from 40 to 81 years, average age 61	
5. Religion	Protestant 58%; Catholic, 35%; Jewish 2%; others 5%	
6. Menopause	85% postmenopausal, average age at menopause 49.6	
7. Race	White 99%; Negro 1%	
8. Family history of cancer	10.3%	
9. Delay in diagnosis		
10. Malignancy elsewhere	9.3%	
11. Previous hormone therapy	1 case or 0.5%	
12. Previous radium or x-ray	2:184—1%	
13. Associated pathology:		
A. Diabetes		8.1%
B. Obesity		
C. Hypertension		37%
D. Fibroids		18%
E. Endometriosis		4%
F. Granulosa-cell tumor of ovary		0
14. Symptomatology:		
A. Postmenopausal bleeding		85%
B. Pain		27%
C. Vaginal bleeding		26%
D. Intermenstrual bleeding		13%
E. Pressure		3%

Race.—Ninety-nine per cent of our patients were white, 1 per cent Negro.

Family History of Cancer.—There was a family history of cancer in 10.3 per cent of the women in this series. Hertig reported that 12 per cent of his series had a family history of cancer. Brobeck[13] in 1949 noted a significant increase of corpus cancer in the mothers and sisters of patients who had this disease when compared with relatives of normal women.

Delay in Diagnosis.—Fifty-seven per cent of our group delayed 0 to 9 months in seeking medical care and, of these, 50 per cent survived five years or more. Thirty-one per cent delayed 10 to 19 months in seeking medical care and 50 per cent of these survived five years or more. Seven per cent of the patients delayed 20 to 29 months in seeking medical care and, strangely enough, 76 per cent of these survived five years or more. Two per cent delayed 30 to 39 months and, of these, 50 per cent survived five years or more. From these observations, one must conclude that carcinoma of the corpus is a slow-growing form of neoplasm.

Malignancy Elsewhere.—There was an additional primary malignancy noted in 9.3 per cent of our cases. This is in contrast to our group of cervix cancers, in 3 per cent of which there was malignancy elsewhere. We believe that

this difference can be accounted for by the fact that cancer of the uterine corpus occurs in an age group that is on the average ten years older.

Warren and Gates,[14] Ettinger,[15] and others, have stated in the past that they believe that multiple malignancy occurs more frequently than can be explained on the basis of chance alone.

History of Previous Hormone Therapy.—One of our patients, or 0.5 per cent of the total, had a history of prolonged estrogen ingestion. It is possible that others of our patients received estrogen for a prolonged period prior to the development of corpus cancer, but we have no documentary evidence of this.

There are several reports in the recent literature which seem to point up a relationship between the injudicious prolonged use of estrogens and the subsequent development of corpus cancer. However, Novak[16] feels that in these reports the prolonged estrogen administration may represent a superimposed factor on an already existing predisposition to the development of cancer.

History of Previous Radium or X-ray.—Two of our 184 patients, or 1 per cent, had been previously irradiated for benign uterine bleeding.

Corscaden[17] in studying 958 patients who were treated for benign uterine bleeding by the radiotherapeutic menopause, observed that 9, or approximately 1 per cent, subsequently developed corpus carcinoma. He believed, however, that the abnormal uterine bleeding prior to the menopause, rather than its treatment with irradiation, was the factor that predisposed to the future development of carcinoma of the uterine corpus. Scheffey[18], too, in studying 124 patients with corpus cancer, 12 of whom had received irradiation therapy for supposedly benign lesions, concluded that the irradiation therapy was not the responsible factor in the subsequent occurrence of the malignancy.

Associated Pathology.—

A. Diabetes: Eight and one-tenth per cent of our patients suffered from diabetes. Other men report a similar incidence: Moss,[19] 11 per cent, Hertig,[8] 9 per cent, and Way,[20] 14 per cent.

Spiegelman and Marks[21] observed that in a study of over one million women from the general population in corresponding age groups, only 1 per cent had diabetes. This study indicates an increased incidence of diabetes in women with carcinoma of the uterine corpus. Marble,[22] however, thought that the diabetes was related to the obesity so commonly found in women with carcinoma of the corpus, rather than to the carcinoma itself.

B. Obesity: Our records are not complete for these years with respect to height and weight. We have the distinct impression that obesity was present in at least a large majority of the cases. Hertig[8] reports 44 per cent obesity, Palmer[2] 74 per cent. It is generally conceded that there is an increased incidence of obesity in women with carcinoma of the corpus.

C. Hypertension: Thirty-seven per cent of the series had a blood pressure over 140/90. This figure does not seem remarkable in a group of women whose average age is 61, for Master,[23] studying 6,000 women over the age of 40, found 40 per cent between the ages of 40 and 49 would have a blood pressure 140/90 or over.

D. Fibroids: Eighteen per cent of the patients in this group had associated fibroids of the uterus. Peightal[10] reports 36 per cent co-existing fibroids in women with corpus cancer, Henriksen[24] 22 per cent, and Hertig[8] 38 per cent.

Some writers have interpreted the association between fibroid and carcinoma of the corpus as evidence of hyperestrinism. However, since Corscaden[3] has observed that approximately 40 per cent of the women in this age

group can be expected to have uterine fibroids, it is evident that no unusual relationship exists between uterine fibroids and cancer of the uterine corpus.

E. Endometriosis: Four per cent of these women had an associated endometriosis. This figure is what might be expected, based on the incidence of endometriosis in similar age groups. Holmes[25] found no corpus cancer complicating his group of cases of endometriosis.

F. Granulosa-cell Tumor: None of our patients had an associated granulosa-cell tumor of the ovary. However, it has been noted, as pointed out by Hertig,[8] that corpus cancer accompanies the estrogenic ovarian tumors, namely, the granulosa- and theca-cell types, in 20 per cent of the cases. This fact supports the contention of those who believe that excess estrogen stimulation is an important etiological factor in the development of corpus cancer.

Symptomatology.—The most common symptom observed in our patients was postmenopausal bleeding, which occurred in 85 per cent of the cases. This is in agreement with most published reports. The most common cause of postmenopauseal bleeding, however, is cancer of the cervix, as shown by Kanter and Klawans.[26] They found that 52 per cent of the cases of postmenopausal bleeding observed in their clinic were diagnosed as cancer of the cervix, while only 11 per cent were due to cancer of the corpus.

Other symptoms noted in our study were pain, 27 per cent; vaginal discharge, 26 per cent; intermenstrual bleeding, 13 per cent; and pressure, 3 per cent.

Clinical Classification

We used the two main subdivisions of the clinical classification suggested in the sixth volume of the *Annual Reports on the Results of Radiotherapy in Carcinoma of the Uterine Cervix*[27]:

Stage I. The growth is confined to the uterus (operable).
Stage II. The growth has spread outside the uterus (inoperable).

We did not subdivide Stage I into clinically operable and technically operable cases as the classification suggests.

Eighty-five per cent of our cases were Stage I and 15 per cent were Stage II.

Histologic Type

Ninety-five per cent of our cases were adenocarcinoma, 5 per cent were typed as adenoacanthoma. Novak[28] states that adenoacanthoma represents squamous metaplasia in either the surface or the gland epithelium in adenocarcinoma.

Histological Grade

All of the microscopic sections in this group of cases were graded as to degree of malignancy by our former pathologist, Dr. B. Earle Clarke. He used a slight modification of the method of grading suggested by Healy.

Our cases were divided into three grades, the main criteria of which were:

Grade I. (a) Papillar adenoma malignum—localized polypoid proliferation, glandular architecture preserved, slight degree of anaplasia, extension beyond basement membrane, no invasion of myometrium.

(b) Adenoma malignum—same as (a) but involving a more extensive area of the endometrium.

Grade II. Adenocarcinoma—slight preservation of glandular architecture, greater degree of anaplasia, invasion of myometrium.

Grade III. Anaplastic carcinoma—no preservation of glandular architecture, extreme degree of anaplasia, invasion of myometrium and surrounding tissues.

Thirty-nine per cent of our cases were Grade I, 30 per cent were Grade II, and 14 per cent Grade III. The remaining 17 per cent of the cases could not be graded accurately due either to the small amount of tissue available for microscopic study or to advanced degenerative changes in the tissue.

Methods of Treatment

The standard method of treatment in this clinic has involved the use of preoperative intracavitary radium in tandem, followed in six weeks by an abdominal panhysterectomy with complete removal of the adnexa and a generous portion of the vaginal cuff.

In the early years, we had available 25 and 50 mg. radium sources, filtered by 0.5 mm. of silver and 1.0 mm. of brass. These were placed in tandem in a rubber sheath. The amount employed and the duration of use depended on the size of the uterus.

In recent years we have used 25 mg. radium sources, filtered by 0.5 mm. of platinum, placed in tandem in a brass capsule. In the average case, 100 mg. are in place for 30 to 36 hours with an average dose of 3,000 to 3,600 mg. hr.

Fifty-three per cent of our cases were treated by this standard plan. Twenty-two per cent of our cases were treated by radium alone, 17 per cent by hysterectomy alone, 5 per cent by hysterectomy followed by irradiation, 2 per cent by x-ray alone, and 1 per cent received no treatment.

Results of Treatment (1936 to 1945)

Seventy-two of the 126 patients, or 57.1 per cent, were alive and well at the end of five years. As shown by Table III, we have attempted to study the

TABLE III. A STUDY OF FIVE-YEAR SURVIVALS IN 126 PATIENTS WITH CANCER OF THE UTERINE CORPUS

WITH RESPECT TO	PERCENTAGE DISTRIBUTION		FIVE-YEAR SURVIVALS	
	NO.	%	NO.	%
Clinical Stage.—				
Stage I	107	85	69	64.4
Stage II	19	15	3	15.9
Totals	126	100	72	57.1
Histological Grading. —				
Grade I	49	39	31	61
Grade II	37	30	22	59.4
Grade III	18	14	6	33.0
Not classified	22	17	13	59
Totals	126	100	72	57.1
Histological Type.—				
Adenocarcinoma	120	95	68	56.7
Adeno-acanthoma	6	5	4	66.6
Totals	126	100	72	57.1
Type of Treatment.—				
Radium followed by hysterectomy	67	53	41	61
Radium alone	28	22	12	43
Hysterectomy alone	22	17	15	68
Hysterectomy followed by radium (2), x-ray (4)	6	5	4	67
X-ray alone	2	2	0	0
No treatment	1	1	0	0
Totals	126	100	72	57.1

effect of the clinical stage, the histological grade, the histological type, and the type of treatment on the five-year survival rate.

When the disease was confined to the uterus, as it was in 85 per cent of our cases, 64.4 per cent of our patients survived five years or more. When the disease had spread beyond the confines of the uterus, as it did in 15 per cent of the cases, only 15.9 per cent of the patients survived five years or more.

The degree of anaplasia and presence of invasion obviously has an adverse effect on the five-year survival rates as demonstrated by the following figures: In lesions classified as Grade I, 61 per cent survived five years or more; in Grade II lesions 59.4 per cent survived five years or more, and in Grade III only 33 per cent were five-year survivors.

The cases classified as adenocarcinoma, representing 95 per cent of the total, had a 56.7 per cent five-year survival rate. Adenoacanthoma yielded the slightly better five-year survival rate of 66.6 per cent. Novak[28] noted the relatively favorable results generally seen in the adenoacanthomatous group and attributed it to the fact that, in his experience, adenoacanthomatous changes ar seen in the adenocarcinomas of lesser degrees of malignancy.

According to our figures, the most favorable type of treatment would seem to be hysterectomy alone, for 68 per cent of these survived five years or more as compared with a 61 per cent five-year survival rate in the group treated with radium followed by hysterectomy. We feel, however, that this can be explained by the fact that the group treated by hysterectomy alone is a much smaller group and, in addition, a much more favorable group. Ninety per cent of these were clinical Stage I as compared with the 85 per cent over-all figure for Stage I. Only 43 per cent of the patients treated by radium alone survived five years or more. The remaining groups are too small to be of any statistical significance.

Recurrence

Sixteen of the 126 patients, or 12.6 per cent, suffered a recurrence that first appeared six months or more after the initial treatment. This figure coincides with that report by Finn,[29] who in a series of 266 patients reported that 14 per cent suffered recurrence of the disease.

A breakdown of our figures showed that the cancer had a lesser tendency to recur in the lesions of lower histological grade (6 per cent recurrence) and in the lesions confined to the uterus (11 per cent recurrence) than in the histologically more anaplastic lesions (28 per cent recurrence) and in the lesions that had extended beyond the uterus (21 per cent recurrence).

Results From Other Clinics

We have studied the five-year survival rates reported by various clinics that treat cancer of the corpus in order to evaluate our methods of treatment.

The three most commonly used methods of treating this disease are (1) radium alone, (2) hysterectomy alone, and (3) a combination of preoperative radiation and hysterectomy.

(1) Radium alone, using either the tandem, mechanical devices, or the packing technique proposed by Heyman,[30] yields five-year survival rates ranging from 20 to 62 per cent with an average of 50 per cent. Best results are obtained with the packing technique. Table IV shows five-year survival rates with the use of radium alone as published by several clinics.

(2) Hysterectomy alone, representing a complete removal of the uterus, the adnexa, and usually a generous portion of the vaginal cuff, yields approximately 40 to 84 per cent five-year survivals, as shown by Table V. The average five-year survival rate by this method of treatment is 60 per cent.

TABLE IV. FIVE-YEAR SURVIVAL RATES IN CORPUS CANCER TREATED BY RADIUM ALONE

AUTHOR	NO. OF CASES	FIVE-YEAR SURVIVAL RATE
Heyman[31] (packing)	459	62%
Corscaden[32] (tandem or mechanical device)	27	48%
Taylor and Becker[33] (tandem)	60	47%
Heyman[31] (tandem)	158	45%
Rhode Island Hospital (tandem)	28	43%
Healy and Brown[5] (radon tandem)	96	39%
Arneson[34] (multiple sources)	43	27%

TABLE V. FIVE-YEAR SURVIVAL RATES IN CORPUS CANCER TREATED BY HYSTERECTOMY ALONE

AUTHOR	NO. OF CASES	FIVE-YEAR SURVIVAL RATE
Arneson[34]	18	84%
Rhode Island Hospital	22	68%
Masson[35]	306	67%
Taylor and Becker[33]	17	65%
Norris and Dunne[36]	115	49%

(3) Combination of preoperative radium or x-ray or both, followed in 6 to 8 weeks by complete hysterectomy, yields approximately 50 to 85 per cent five-year survivals with an average of about 70 per cent. Table VI shows survival rates of various authors using this type of treatment.

TABLE VI. FIVE-YEAR SURVIVAL RATES IN CORPUS CANCER TREATED WITH RADIATION FOLLOWED BY HYSTERECTOMY

AUTHOR	METHOD OF APPLICATION	NO. OF CASES	FIVE-YEAR SURVIVAL RATES
Hundley[9]	Multiple capsules preoperatively; x-ray postoperatively	32	84%
Heyman[30]	Packing technique, preoperatively	65	78%
Miller[37]	X-ray preoperatively	36	77%
Corscaden[32]	Tandem or mechanical device preoperatively	25	72%
Taylor and Becker[33]	Multiple capsules preoperatively	31	65%
Rhode Island Hospital	Tandem preoperatively	67	61%
Healy and Brown[5]	Radon tandem preoperatively	93	55%

Comment on Methods of Treatment

Radium alone.—

An evaluation of the five-year survival rates of patients treated with radium alone demonstrates that the packing technique utilizing multiple small sources of radium, sometimes in two separate applications, offers the best chance for cure. However, study of the uteri removed after previous treatment with intrauterine radium reveals residual cancer in from 50 to 90 per cent of the cases as shown by Table VII.

TABLE VII. PERCENTAGE OF RESIDUAL CANCER IN UTERI FOLLOWING TREATMENT WITH INTRACAVITARY RADIUM

AUTHOR	METHOD	PERCENTAGE RESIDUAL CANCER
Donovan and Shields[38]	Tandem	90
Corscaden[32]	Tandem or mechanical device	76
Waterman[39]	Tandem	73
Hundley[9]	Multiple capsules	72
Palmer[2]	Tandem	70
Scheffey[40]	Multiple capsules	56
Taylor and Becker[33]	Multiple capsules	50

Sampson,[41] in 1934, showed diagrammatically that because of the normal variations in the size and the shape of the uterine cavity, intrauterine radium by the tandem method could not deliver a cancerocidal dose to all portions of the uterine mucosa.

Corscaden[3] stated that even with the most efficient method of applying radium to the uterine cavity there will be viable tumor left in 30 per cent of the cases because up to the present time there is no method capable of delivering a cancerocidal dose to distant areas in the myometrium and on the surface of the uterus.

The use of radium alone in the treatment of carcinoma of the uterine corpus seems to be justified only in poor-risk patients.

Surgery Alone.—

Although in our own study and in the study of Arneson[34] the most favorable five-year survival rate was obtained in those cases treated by surgery alone, we feel that this was due to selection of favorable cases for this method of treatment.

Some clinics are suggesting the use of radical surgery such as the Wertheim operation, especially when the disease has extended to the cervix with the possibility of involvement of the ureteral, obturator, and hypogastric glands. This suggestion merits serious consideration in view of the fact that Randall[42] found viable-looking carcinoma on section of the iliac nodes in 20 per cent of 20 cases five or six months following radium therapy.

Peightal[10] stated that best results in the future will be obtained by a more radical type of surgery followed by a two-staged extraperitoneal lymph node dissection employing the inguinal approach.

Radium Followed by Hysterectomy.—

Considering the disadvantages of the use of radium alone, such as the poorer survival rates and the higher percentages of residual cancer in the extirpated uteri, it is obvious that this method is not definitive in the treatment of cancer of the corpus uteri. The use of surgery alone has the disadvantage of an increased incidence of recurrence in the vaginal vault and abdominal wall.

It is our opinion after this review of our own and the results reported by others that the method of choice in the treatment of this disease is preoperative intracavitary radium by the packing technique, followed in 6 to 8 weeks by the complete removal of uterus, adnexa, and a generous portion of vaginal cuff.

Summary

Cancer of the corpus uteri has been studied by reviewing 184 cases seen at the Rhode Island Hospital between the years 1922 and 1945.

The relative frequency and the influence of marital status, parity, economic status, age, religion, menopause, color, heredity, delay in diagnosis, multiple cancer, previous hormone therapy, and previous irradiation have been discussed.

The incidence of associated conditions, such as obesity, diabetes, hypertension, etc., has been studied. The symptomatology has been noted.

Our criteria for clinical classification, histological type, and histological grade have been stated. Methods of treatment have been described, and results of treatment in 126 patients seen between the years 1936 and 1945 have been presented.

Results from other clinics have been studied and evaluated and conclusions have been drawn as to the most effective methods of treating this disease.

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INTRAVENOUS VERATRUM VIRIDE IN THE TREATMENT OF TOXEMIA OF PREGNANCY

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THE use of veratrum viride in the treatment of toxemia of pregnancy has been both favorably and unfavorably reported in the literature.[1, 2, 3, 4] The chief criticism of the drug has been the lack of standardization of the active principles and its so-called toxic effects. Despite these disadvantages, investigations have continued with its use in the treatment of toxemia and hypertension with encouraging results. The pharmacology of the drug is still not entirely understood, but attempts are being made to fractionate the crude complex preparation into its active hypotensive components.[5] Assali[2] in 1950 advocated and standardized the dosage for intravenous Veratrone. By keeping the dosage low he was able to depress blood pressure in most toxic patients with minimal side effects.

In this hospital, which has 6,000 deliveries per year, 98 per cent of the patients are private and are treated by both specialists and general practitioners. No rigid rules have been set up for the management of toxemia, and, as a result, a variety of methods is employed. The most commonly used treatment has been a modification of the Stroganoff method (morphine, magnesium sulfate, and barbiturates).

The use of heavy sedation for the control and prevention of convulsions is classic and the most common therapy in use, but admittedly adds to the complexity of management of a seriously ill patient, and if used injudiciously may further endanger life.

Treatment of mild toxemia with bed rest, low sodium diet, and mild sedation has given consistently good results and poses no problem. To the contrary, results in the treatment of severe toxemia have not been satisfactory and have prompted a trial use of intravenous Veratrone in this hospital.

Material and Method

During the period from December, 1950, through April, 1952, 68 patients with toxemia were admitted for treatment, an incidence of 0.8 per cent. Twenty-eight per cent were considered to have severe pre-eclampsia and eclampsia.

Ten cases of this series were selected for treatment with intravenous Veratrone.* All patients in this group had either severe pre-eclampsia or eclampsia. Each patient was examined by one or more consultants and the diagnosis confirmed. A complete medical and obstetrical history was obtained, and a physical examination was done with special attention to abnormalities of the eye

*The veratrum viride preparation used in this study was Veratrone, Parke, Davis & Company, furnished through the courtesy of Dr. E. C. Vonder Heide.

grounds, heart, and lungs. Routine laboratory studies were carried out, and an accurate record of fluid intake and urinary output was made. Table I is a brief summary of some of the pertinent data in relation to these ten cases.

TABLE I

CASES	GESTATION IN WEEKS	PARITY	METHOD OF DELIVERY	CLASSIFICATION
1	26	Multipara	Spontaneous	Eclampsia
2	30	Multipara	Forceps	Pre-eclampsia
3	26	Primipara	Spontaneous	Eclampsia
4	36	Multipara	Section	Eclampsia
5	40	Primipara	Forceps	Eclampsia
6	31	Multipara	Spontaneous	Pre-eclampsia
7	30	Multipara	Forceps	Pre-eclampsia
8	40	Primipara	Section	Pre-eclampsia
9	36	Multipara	Spontaneous	Pre-eclampsia
10	38	Primipara	Spontaneous	Pre-eclampsia

In the majority of selected cases, other methods of treatment had been used but resulted in no clinical improvement, as was evident by continued rise in blood pressure and recurring convulsions. Most of the cases were treated by the technique described by Assali[2] with slight variations. Nearly all the patients received the crude unsterile Veratrone, but recently the sterile preparation has been made available for use. The patient is given an initial intravenous dose of 0.2 ml. of Veratrone, diluted in 1 ml. of 5 per cent glucose. The drug is given slowly over a period of three minutes. Initial drop in blood pressure begins within five minutes, is dramatic, and usually lasts from 45 minutes to one hour, after which time it slowly climbs to former high levels. Subsequent to the initial dose, the drug is administered by intravenous infusion in 5 per cent glucose in water with the rate regulated so as to deliver an hourly amount of 0.2 ml. of Veratrone. Careful check must be made every hour on the blood pressure and pulse, and adjustments made in the rate of flow according to response. The patient receives no other drug or treatment other than mild sedation with barbiturates.

Results

The following four cases are discussed in detail with graphic illustrations.

CASE 1.—The patient was a 38-year-old gravida vi, para iv, white woman who was in her twenty-fourth week of gestation. She had received no prenatal care and was admitted in semicomatose condition following a convulsion at home. There was no history of previous toxemia.

Examination revealed a slightly cyanotic, semicomatose white woman in acute distress. Upon admission blood pressure was 210/120, pulse 50 per minute, and respirations 18 per minute. Fundoscopic examination was negative. The abdomen was enlarged to the size of a six months' pregnancy and the fetal heart tones were heard in the right lower quadrant at 140 per minute. There was no edema present. The remainder of the physical examination was negative.

Initial laboratory findings revealed a 4 plus albuminuria, with two to three finely granular casts per high-power field. The white count was 19,250 with a normal differential, but the red count and hemoglobin were normal. Nonprotein nitrogen was 47 mg. per cent, urea nitrogen 28 mg. per cent, uric acid 4.4 mg. per cent, and carbon dioxide combining power was 54 volumes per cent.

A diagnosis of eclampsia was made.

Modified Stroganoff treatment was started and continued for 57 hours. During the first 34 hours of this therapy the blood pressure fluctuated between 150/180 and

100/120 but then continued to rise, and for the next 23 hours averaged 220/130 in spite of heavy sedation. It was then decided to begin treatment with intravenous Veratrone. Following the initial injection continuous intravenous drip was employed for the next 14 hours. During this time the blood pressure ranged about 140/90 with very little fluctuation. After twelve hours of control, labor was induced with Pitocin and one and one-half hours later the patient delivered a stillborn infant. The intravenous drip was terminated two and one-half hours after delivery and was not reinstituted. The side effects of this twelve hours of therapy were minimal. Within an hour after the continuous drip was discontinued the blood pressure had returned to 190/120. Following delivery, sedation with barbiturates and magnesium sulfate was used to control blood pressure. The systolic pressure remained near 200 mm. the first day and then gradually fell to 170 over a diastolic of 100 on the twelfth postpartum day when she was discharged. Eight weeks after delivery blood pressure was 160/100 and urinalysis showed a trace of albumin.

Intravenous Veratrone was used because of poor response to heavy sedation and fear of recurrent convulsions. Treatment resulted in good control of hypertension and symptoms in a patient who had eclampsia with an underlying hypertension.

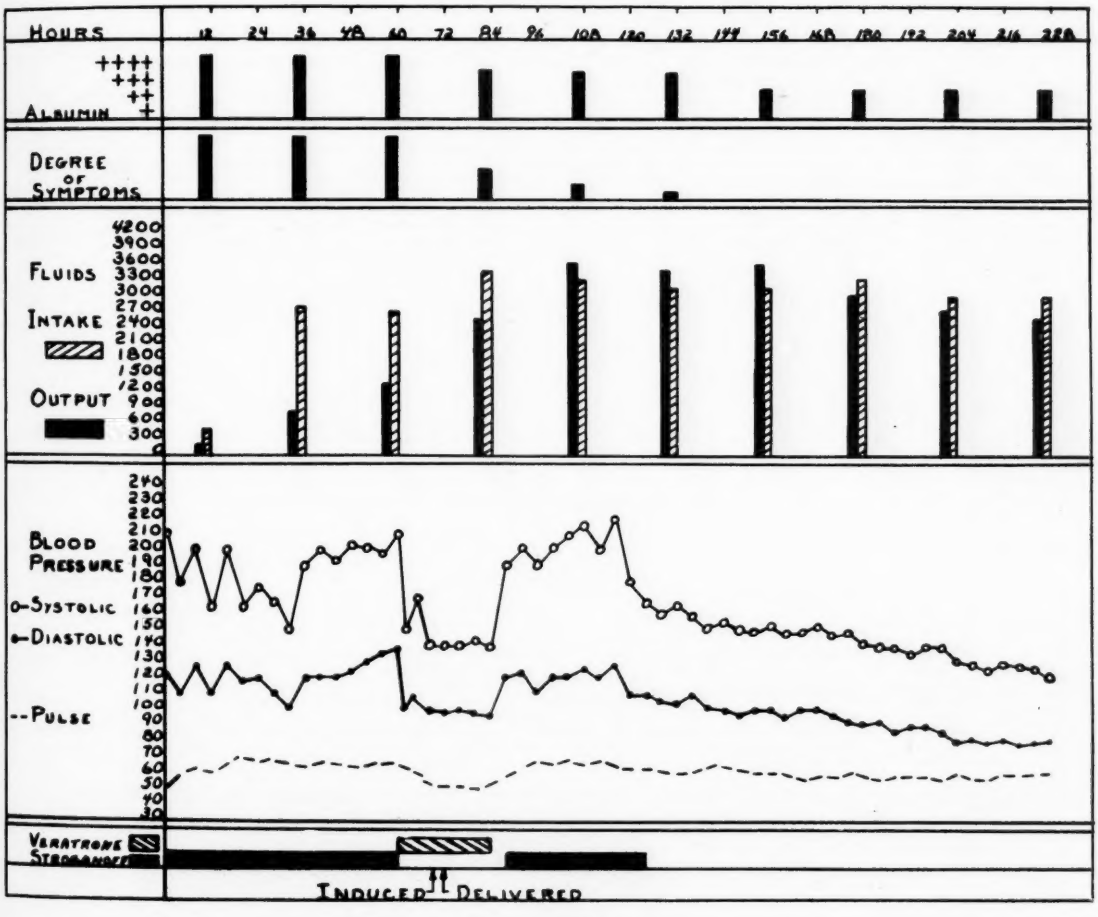

Fig. 1.—Case 1.

CASE 2.—A 35-year-old gravida v, para iv, white woman was admitted in her thirtieth week of gestation, complaining of blindness of six hours' duration. According to the attending physician, ankle edema, albuminuria, and hypertension had been progressive for a month prior to admission. Past history revealed that she had a toxemia with her first pregnancy.

Examination revealed an acutely ill woman, who was semicomatose but rational. There was marked edema present of the face, eyes, and extremities. She was able to distinguish light but not objects. Retinal examination revealed marked arterial spasm but no hemorrhages. The abdomen was enlarged to the size of a seven months' pregnancy and the fetal heart tones were of good quality in the left lower quadrant. There was 4 plus edema to the knees. The blood pressure upon admission was 200/130. The remainder of the physical examination was negative.

Initial laboratory studies revealed 4 plus albuminuria and occasional fine granular casts. The blood count was normal. Nonprotein nitrogen on admission was 35 mg. per cent.

A diagnosis of severe pre-eclampsia was made.

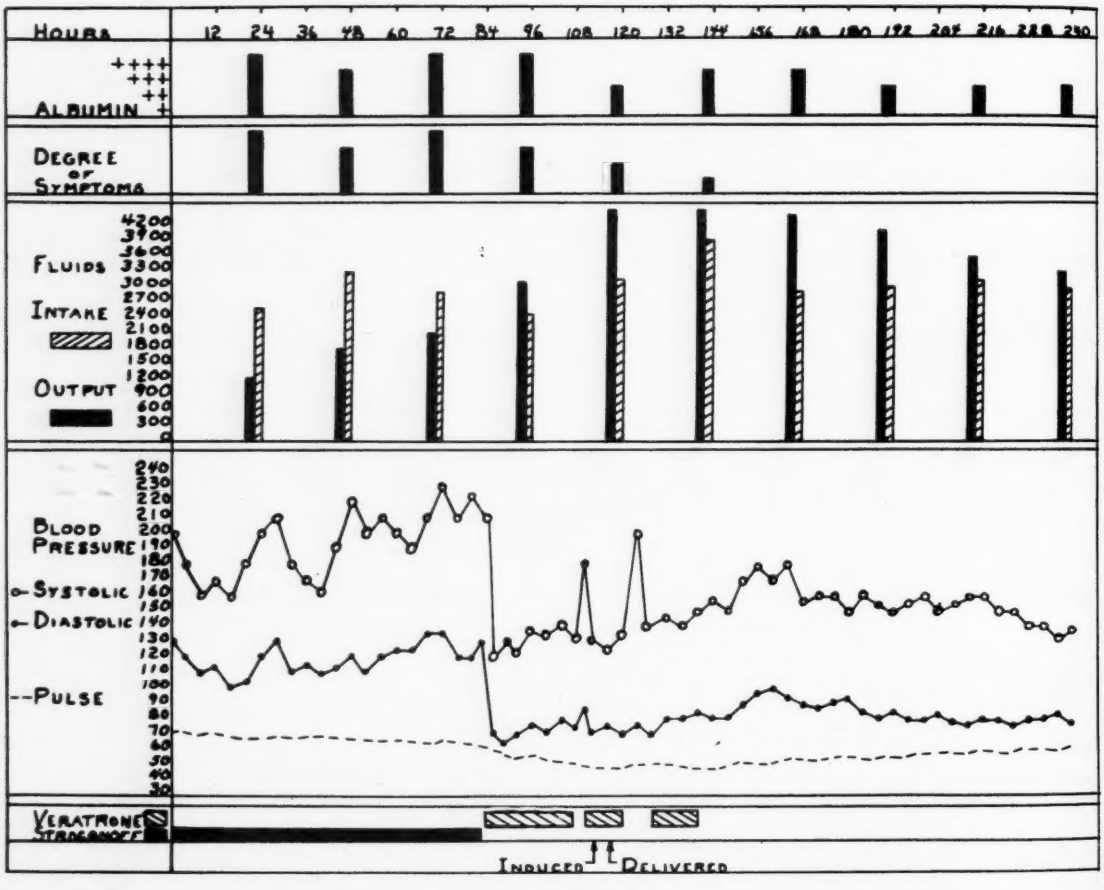

Fig. 2.—Case 2.

The patient was started on a modified Stroganoff regime, improving slightly during the first twenty-four hours. After forty-eight hours of this therapy the patient's condition gradually became worse, and by the third day the headaches and blindness had returned. The blood pressure at this point was 230/130. In view of her poor response, intravenous Veratrone was started eighty-five hours after admission, and within five minutes her blood pressure was 140/70. Subjective symptoms from the Veratrone were minimal. Following the initial injection, continuous drip was begun and maintained for the next forty hours. During this time all other medication was discontinued and the blood pressure averaged 130/90. Within eight hours after Veratrone therapy all toxic symptoms had cleared. Pitocin induction was started after twenty-eight hours of control with Veratrone, and four hours later the

patient delivered a stillborn infant. The continuous intravenous Veratrone was maintained for another twelve hours, after which time the symptoms were controlled with Sodium Amytal, 1½ grains four times daily. Five more days of hospitalization resulted in steady improvement, and the patient was discharged on the eleventh hospital day with a blood pressure of 156/70 and 2 plus albuminuria. Her checkup at 6 weeks revealed a trace of albumin and a pressure of 120/70.

This patient showed an excellent response to Veratrone with improvement shortly after therapy was begun. During the entire forty hours of treatment her blood pressure remained at normal levels. She required no sedation, and no oliguria was noted.

CASE 3.—A 16-year-old primigravida without prenatal care was admitted in her twenty-sixth week of gestation following a convulsion at home. For five days prior to admission she had noted progressive headaches, nausea and vomiting, vertigo, and spots before the eyes.

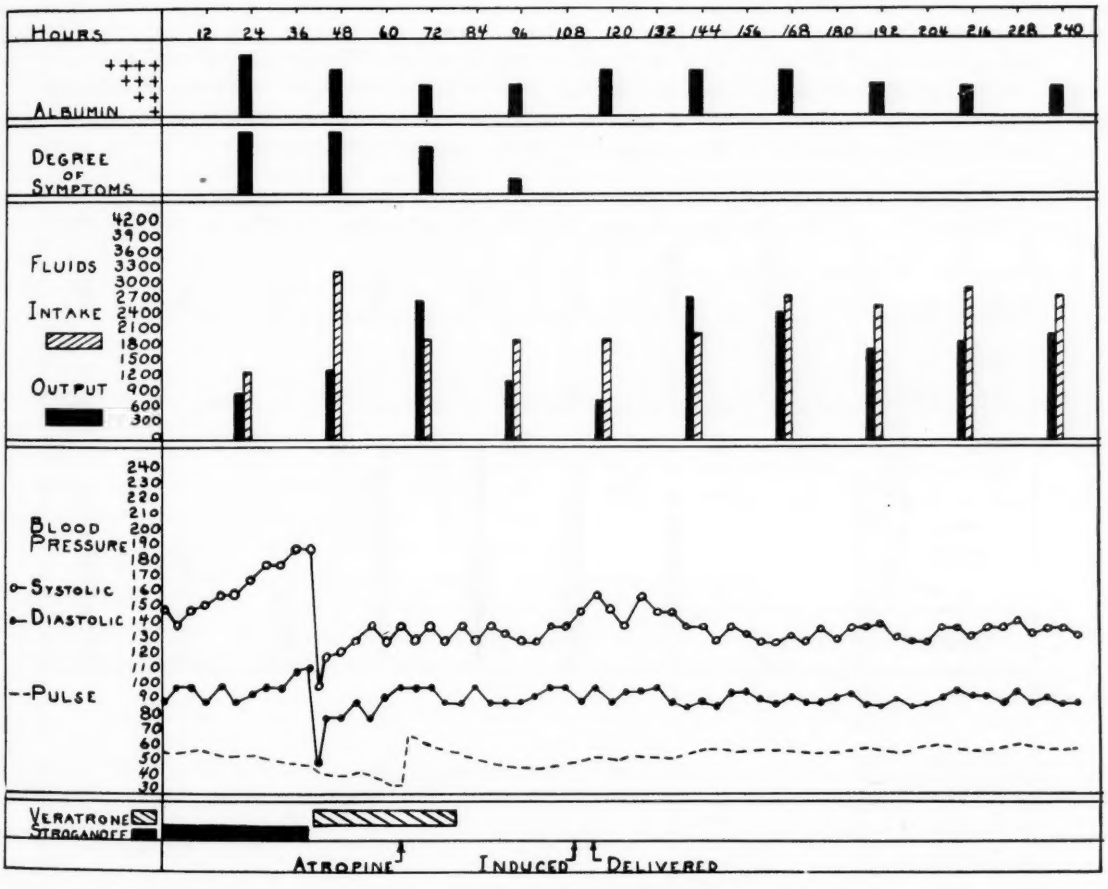

Fig. 3.—Case 3.

Examination revealed a lethargic white girl in acute distress. There was periorbital edema present. Fundoscopic examination was normal except for moderate vasoconstriction. Blood pressure was 150/90 and pulse was 60 per minute. The heart and lungs were not remarkable. The uterus was enlarged to the size of a six months' pregnancy with good fetal heart tones head in the right lower quadrant. There was no evidence of peripheral edema.

Initial laboratory studies revealed a normal red and white count. The urinalysis showed 4 plus albumin and 10 to 20 finely granular casts per high-power field. The nonprotein nitro-

gen was 32 mg. per cent and the uric acid was 3.9 mg. per cent. Hematocrit was 35 per cent and the carbon dioxide combining power was 56 volumes per cent.

A diagnosis of eclampsia was made.

The patient was given magnesium sulfate and morphine for sedation. For the first thirty-six hours her blood pressure remained about 140/90, and then gradually began to rise during the next seven hours until it reached 190/120. At this point treatment with intravenous Veratrone was begun. The usual initial dose of 0.2 ml. was given and in five minutes the blood pressure was 120/50, and was maintained at this level for one hour. At the end of this time a continuous intravenous drip was begun, delivering approximately 0.2 ml. per hour. This was continued for the next 34 hours, regulating the pressure between 130/150 and 80/100. After nineteen hours of continuous therapy her pulse rate was 36. An electrocardiogram revealed a sinus bradycardia. Atropine, 1/150 grain was administered and in a matter of minutes the pulse rate had returned to 68 per minute. There was no elevation in the blood pressure. After thirty-four hours of control with intravenous Veratrone the therapy was temporarily interrupted. Since the pressure did not return to its former level it was felt that this patient could be maintained on Vertavis and sedation. Blood pressure and symptoms were controlled for sixty-six hours and then medical induction begun. A premature infant was delivered six hours later, but survived only five hours. Following delivery the patient continued to improve with sedation and Vertavis. She was discharged on the twelfth post-

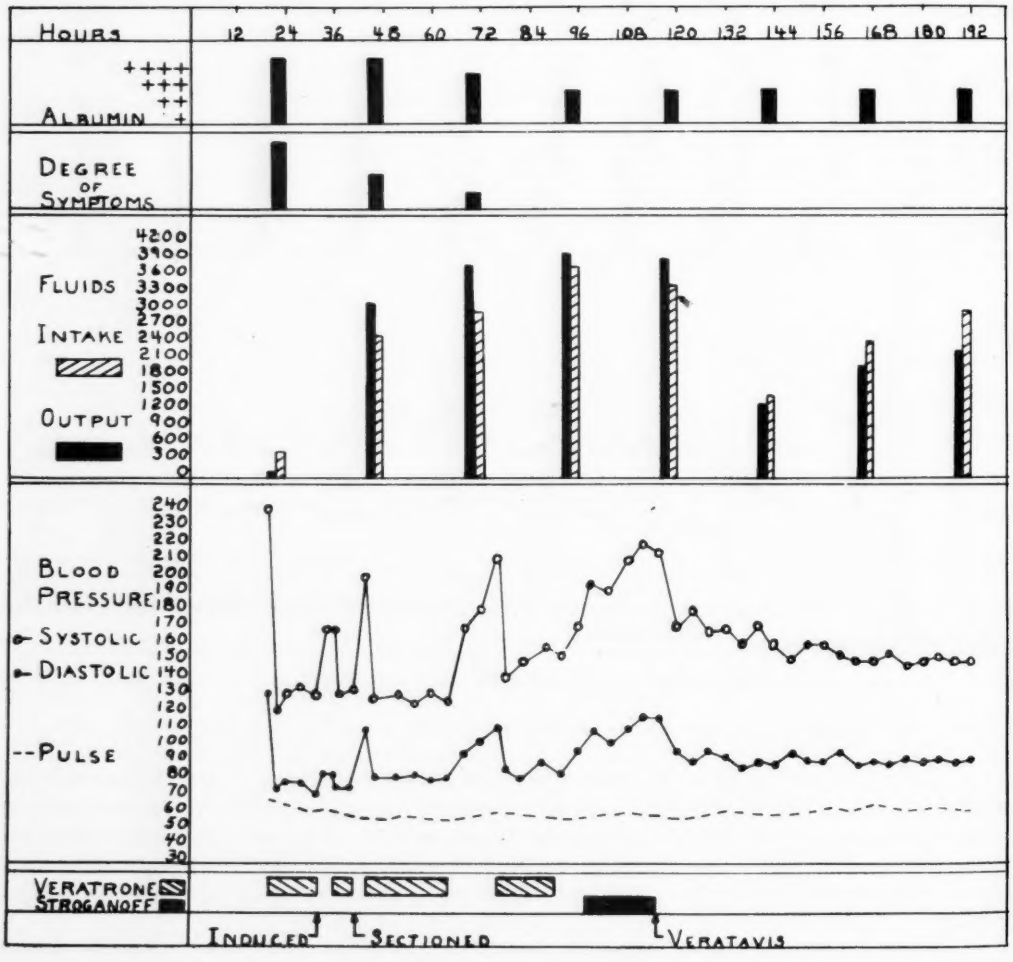

Fig. 4.—Case 4.

partum day with 1 plus albumin and a pressure of 120/80. Examination three and six weeks after discharge revealed a normal blood pressure and urinalysis, and a phenolsulfonphthalein excretion of 60 per cent.

This patient had severe eclampsia which did not respond to the modified Stroganoff regime. Therefore she was given intravenous Veratrone for thirty-four hours with complete control of blood pressure and symptoms.

CASE 4.—A 40-year-old gravida iv, para iii, Negro woman was admitted through the emergency room following a convulsion at home. She was in the thirty-sixth week of gestation and had received no prenatal care. Three previous pregnancies had been uncomplicated. The patient had another convulsion on admission to the emergency room.

Examination revealed an obese Negro woman appearing acutely ill. She was semicomatose and somewhat irrational. Blood pressure was 240/130 and the pulse was 80. There was 2 plus edema of the lower extremities. The uterus was enlarged to the size of an eight months' pregnancy. The fetal heart tones were 132 per minute in the right upper quadrant. The remainder of the physical examination was negative.

Initial laboratory studies revealed a 4 plus albuminuria, with 10 to 15 white blood cells in the catheterized specimen. Sugar and acetone were negative. The blood count was normal. Nonprotein nitrogen was 38 mg. per cent.

A diagnosis of eclampsia was made.

The patient was immediately given 0.2 ml. of Veratrone intravenously and within ten minutes the blood pressure was 120/80, and was regulated at this level for the next thirteen hours by continuous drip. Symptoms and blood pressure being well controlled by this time, a medical induction was begun after rupture of the membranes. Labor failed to begin after twenty-one hours so the pregnancy was terminated by a low cervical cesarean section under local anesthesia, with delivery of a living female infant who survived. The intravenous Veratrone was continued for the next nineteen hours, but as soon as it was discontinued the blood pressure began to rise. The patient was given another 1,000 ml. infusion of 5 per cent glucose containing 1.5 ml. of Veratrone which regulated her pressure normally for the next thirteen hours. Following this she was given 5 Craw units of oral veratrum four times daily, and during the remainder of her hospital stay the blood pressure was 170/110. When last seen, three weeks after delivery, her blood pressure was 140/80, nonprotein nitrogen was normal, and urinalysis revealed one plus albuminuria.

This patient was immediately started on intravenous Veratrone. She received a total of forty-three hours of intravenous Veratrone and eighteen hours of the oral veratrum. Her response was excellent and the condition throughout the course of treatment was good. When induction failed, her toxemia was well enough controlled to allow delivery by cesarean section.

Ten cases of severe pre-eclampsia and eclampsia were treated by intravenous Veratrone. Eight of these patients had been treated by other methods with failure of response and an increase in the severity of the symptoms. In contrast, all patients given intravenous Veratrone showed prompt fall and stabilization of the blood pressure and improvement of symptoms which persisted as long as the Veratrone was continued. No appreciable amount of urinary depression was noted, and most patients developed polyuria within twelve hours following the use of the drug. We have not found the degree of urinary depression noted by Willson,[3, 4] but this may be due to our lower dosage of the drug. We have attempted to use the smallest amount of the drug which will keep the blood pressure depressed, and yet avoid drops below normal. The amount of the drug needed is variable, but most patients have responded well to our standard dosage. Symptoms of nausea, flushing of the face, and burning of the throat are commonly experienced by the patient with the initial dose of the drug. We have found these side effects to be variable with the patient. Nausea and vomiting were of such severity in one patient that the drug had to be temporarily discontinued, but in most cases the symptoms are mild

and transitory. By continuous intravenous glucose the patient receives up to 3,000 ml. of fluid in twenty-four hours, furnishing adequate hydration. In some patients with poor veins and marked edema we have had difficulty in maintaining continuous intravenous medication. Using the technique described by Anderson and associates,[6] we have resorted to insertion of polyethylene tubing in an ankle vein. Ten units of heparin are added to each 1,000 ml. of fluid, which although having no effect on the coagulation of blood, seems to prevent or delay the onset of thrombophlebitis. Using this method we have been able to continue intravenous medication in one vein for as long as four days.

Careful observations must be kept of the pulse since, in some patients, marked bradycardia is produced which cannot be differentiated from heart block except by electrocardiogram. In one case the bradycardia was promptly corrected by the use of atropine (Case 3).

Pregnancy is terminated by the most expedient method once the blood pressure has been stabilized, symptoms controlled, and good urinary output established. The period required for stabilization is variable, but no cases were interrupted before a period of at least twelve hours of treatment with the drug.

Induction and delivery from below were carried out in eight cases and delivery by cesarean section in two.

There were no maternal deaths in the entire toxemia series; however, there were ten stillborn infants and three neonatal deaths for a 19.1 per cent fetal mortality. Four of these deaths were in the group of ten cases treated with Veratrone. Three of these cases were of less than seven months' gestation and prematurity was no doubt a major contributing factor.

Table II is a comparison between the mean blood pressure readings prior to and during intravenous Veratrone therapy.

TABLE II

CASES	MEAN BLOOD PRESSURE PRIOR TO INTRAVENOUS VERATRONE	MEAN BLOOD PRESSURE DURING INTRAVENOUS VERATRONE	DURATION OF INTRAVENOUS VERATRONE IN HOURS
1	187/115	134/90	12
2	190/114	132/77	40
3	168/102	119/77	34
4	240/130	132/82	43
5	162/96	131/85	11
6	173/100	134/86	51
7	210/108	142/87	42
8	186/115	140/85	23
9	200/108	148/92	149
10	207/126	146/81	62

Comment

It is understandable how much criticism has been leveled at the use of veratrum viride in the treatment of toxemia. Poor results have come from the injudicious use of the drug which produces marked blood pressure fall, oliguria, and severe side effects. Some investigators are of the opinion that just as good results can be obtained in the treatment of toxemia by other methods of less danger to the patient. Willson[4] believes the control of hypertension in toxemia is of no importance in respect to kidney function, the elevation of the blood pressure being merely a reflection of the toxic state.

We believe that the hypertension is a result of the generalized vasospasm characteristic of the disease, and, unless prompt reduction is obtained, a certain unpredictable number of patients will have cerebral vascular accidents and death. Turner and co-workers[7] found cerebral hemorrhage as a contributing cause of death in eclampsia in one-third of the cases studied.

Regional nerve block has been advocated by a number of investigators as a means of controlling the blood pressure elevation of toxemia. The pressure is lowered by a paralysis of the vasopressor fibers with resultant pooling of blood and reduced cardiac output. In our limited experience, this method has proved to be effective for only short periods of time. Classic methods of control rely on heavy doses of sedation by various drugs. Morphine, barbiturates, and magnesium sulfate are the three drugs in most common usage. Heavy doses of morphine can result in serious depression of the respiratory center of an already edematous brain, causing respiratory embarrassment or even failure. The drug is recognized to produce depression of urinary output and, when used in large doses, as is frequently necessary to control convulsions, has adverse effects on the already toxic unborn baby.

Barbiturates are widely used as central depressants, but, to be effective in severe toxemia, must be used in relatively large doses and are prone to produce pulmonary congestion with resultant pneumonia and cerebral anoxia. Recent studies by McCall and Taylor[8] on cerebral blood flow and oxygen metabolism in toxemia of pregnancy have demonstrated that barbiturates are likely to prolong the coma of eclampsia and add to the morbidity and mortality.

Magnesium sulfate has been found to be the least toxic of the drugs in common usage but likewise requires large doses, and frequently is used in conjunction with morphine and barbiturates.

It is important to have the full cooperation of the severely toxic patient in order to maintain adequate intake of fluid and nourishment, and avoid venous and pulmonary complications. Heavy sedation eliminates all cooperation and only adds to the problem of nursing and medical management of the toxic patient.

We have been impressed with the value of Veratrone in the control of severe toxemia where failure was evident with other methods. Severe hypertension was rapidly reduced to more normal levels, subjective symptoms cleared, and convulsions, when present, were quickly controlled.

We realize this series is small, but results have been sufficiently consistent and favorable to offer encouragement for further use of the drug.

Summary

1. Ten cases of severe pre-eclampsia and eclampsia were treated by the use of intravenous Veratrone.

2. Eight cases had been treated by other accepted methods with no apparent improvement.

3. Side effects of nausea, vomiting, and bradycardia were noted, but were found to be minimal and usually transitory.

4. All patients showed good response to the drug with rapid lowering of hypertension and clearing of symptoms of toxemia within twenty-four hours.

5. Urinary output was diminished at the beginning of use of the drug, but the 24 hour output showed no decrease because of compensatory polyuria.

6. Heavy sedation is avoided and the toxic patient is able to cooperate more fully.

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ECTOPIC PREGNANCY

A Clinical Study of 136 Consecutive Cases

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EXTRAUTERINE pregnancy continues to be one of the first ten causes of maternal deaths in this country. The management of this entity has been reviewed in many publications, but there must be pitfalls in either diagnosis and/or treatment of this abnormal nidation condition for the mortality rate to continue to remain so high. The factors in fatalities due to ectopic pregnancy are: (1) failure of diagnosis, (2) delay in surgery, (3) delay and inadequacy of blood replacement therapy, (4) too extensive elective surgery at the time of laparotomy, and (5) patient's delay in seeking medical care. Of these, the physician is responsible for all but the last factor and thus by being constantly alert to the possibility of ectopic pregnancy, or by being "ectopic pregnancy conscious," he will be able to reduce to a minimum the first four factors.

In a city hospital where indigent patients are cared for, a relatively large number of cases of extrauterine pregnancy will be found, especially when the majority of the female patients are Negroes. In the institution from which this series of cases of extrauterine pregnancy is reported, the treatment of this pathologic condition constituted, during the period of this study, 16.7 per cent of the major operative gynecologic surgery. Noting such a large incidence, a study was undertaken in an effort to analyze tubal pregnancy thoroughly, and to present the unusual difficulties we encountered in our cases.

Analysis of Records—The History

In the 30 month period beginning Jan. 1, 1949, there were 136 consecutive cases of extrauterine pregnancy, proved by pathologic study, and in eight of these there had been a previous tubal pregnancy. Four women in this series died, giving a gross fatality rate of 2.9 per cent. Since only one woman died from causes in any way connected with ruptured tubal pregnancy, this figure is correctable to 0.8 per cent. All cases except one (a fatality) were seen and treated by the Gynecology Staff of the hospital.

In the study were 23 women in whom the pregnancy was their first, 39 who had had only one previous pregnancy, and 74 multiparas, four of whom had had ten or more previous pregnancies.

The ages of the patients ranged from 18 to 40 years, the mean average age being 28.2 years, with 41 per cent of the patients being 30 years of age or older. The predominance of women over the age of 30 agrees with the data of many other authorities[1, 2, 3, 4] and has given rise, in the minds of some, to the specula-

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tion that the ova in these cases might be defective and thus might lend themselves to faulty nidation since these women have passed the age of optimum fertility. Regarding the fertility of this group, over half, i.e., 70 women, gave a history of sterility. The history of sterility of some patients was for ten years or more. The factor of sterility is shown in Table I, which gives the interval of time since the last pregnancy. By perusal of the table, one immediately notes that for the women who had had a previous pregnancy the interval was greater than four years in 54 per cent of the cases.

TABLE I. INTERVAL OF TIME SINCE LAST PREGNANCY

TIME	NO. OF CASES
Less than 6 months	11
7-12 months	18
13-24 months	10
25-36 months	12
4-5 years	31
6-10 years	16
11-15 years	9
16-20 years	5
23 years	1
No previous pregnancy	23
Total	136

This sterility rate is no higher than we would expect because of the predominance, in our study, of Negro patients in whom we find a higher incidence of pelvic inflammatory disease. The report of Nucci[5] gives a 16 per cent rate of temporary sterility in a series of 150 cases, and Siegler[7] noted that two-thirds of the patients in his series had been sterile for an average of three years.

Only a very few studies on the racial incidence have been published, although it is commonly accepted that ectopic pregnancy is much more prevalent in the Negro race. In this study there were only 21 cases in white women, or 15.5 per cent, and 115 cases in Negro women, or 84.5 per cent. When the incidence of ectopic pregnancy on our gynecology service is compared with the incidence of normal pregnancy on our obstetrical service,* which averages 77 per cent Negroes, we find an ectopic-to-normal pregnancy ratio in Negro women of 1:56 and of 1:88 in white women. In a previous study[12] done at this same institution the racial incidence was quite different, for in 393 cases, in a ten-year period, 53 per cent of the patients were white. Langman and Goldblatt[13] reported that at Bellevue Hospital only 11 per cent of the total ectopic pregnancies occurred in the Negro group. The recent report by Anderson[6] gives a true ratio in white women of 1:190 pregnancies and in Negro women 1:130 pregnancies.

A history of pelvic inflammatory disease is very often of little value, since we find that many patients receive antibiotic therapy for alleged pelvic inflammatory disease without the benefit of a thorough pelvic examination and/or proof by other evidences and means of the real existence of salpingitis.

A total of 72 women, or 53 per cent, in our series, have a history indicating infection of the Fallopian tubes and had received therapy for such infection, but pathologic study of the excised tubes revealed there was definite salpingitis of varying stage in only 37 cases, or a true incidence of 28 per cent. This incidence of salpingitis corresponds to that reported by Nucci[5] and Siegler,[7] but is somewhat higher than the figures of Van Etten,[8] MacFarlane and Sparling,[3] and Allen.[9] Thus in only a little more than one-fourth of the total cases could salpingitis definitely be established as the cause of the extrauterine pregnancy,

*The obstetric service serves the same population group in this city as does the gynecology service, namely, the medically indigent women.

which emphasizes that the general impression held by many clinicians, namely, that the majority of tubal pregnancies are the result of an old salpingitis, may not be wholly true. In three-fourths of the cases some other explanation must be sought, such as abnormal motility of the affected tube, congenital malformations of the Fallopian tube, peritubal adhesions, abnormal conditions of the ova, masses in the adnexa and uterus, to list only a few of the other conditions which might impede the progress of the fertilized ova. It seems to us, therefore, that salpingitis, although it is the most definite known cause of tubal pregnancy, can be proved to be actually responsible for only slightly more than one-fourth of the tubal pregnancies in our series, and this point should be clarified in the teaching of medical students.

The past menstrual history, except for the irregularity present, was normal as to interval and duration in all but 16 cases, and in all of these the irregularity was of long duration. A history of amenorrhea, which is one of the classic symptoms in extrauterine gestation, was present in all but 25 cases, or in 81 per cent. In the 25 cases in which there had been no amenorrhea, 9 patients were very positive regarding this fact, while the remaining 16 comprised a group of patients whose menses had been totally irregular, and thus a definite history of amenorrhea could not be established in this latter group.

The time interval since the last menstrual period, in our series of patients, varied from 31 days to an upper limit of 17 months, but in the majority the amenorrhea had been between 42 and 48 days in duration.

Clinical Features

The classical triad of symptoms in extrauterine pregnancy is pain, irregular vaginal bleeding, and syncope. Upon admission, care was taken to obtain the complaints of the patients in their order of importance, so that they could be evaluated as to the time-honored triad. In Table II the chief complaints of the women are listed according to the first and second symptoms as described by the patient, and our findings support the triad.

TABLE II. CHIEF COMPLAINTS ON ADMISSION

	PRIMARY SYMPTOM		SECONDARY SYMPTOM		TOTAL	
	NO. OF CASES	PER-CENT-AGE	NO. OF CASES	PER-CENT-AGE	NO. OF CASES	PER-CENT-AGE
Abdominal pain	91	67	31	23	122	90
Right lower quadrant	20	22				
Left lower quadrant	19	21				
Generalized lower abdomen	52	57				
Irregular vaginal bleeding	22	17	60	44	82	61
Syncope	18	13	24	18	42	31
Nausea and vomiting	3	2	9	7	12	9
Weakness			6	4	6	4
Shoulder pain			3	2	3	0.7
Rectal pain	2	1	2	1	4	2
Anorexia			1	0.7	1	2
Total	136		136			

Shock and a blood pressure of less than 90 mm. of mercury systolic was noted in 33 per cent of our series of cases as admitted, and one hypertensive patient, whose "normal" blood pressure had been 200/100, was admitted in clinical shock with a manometer reading of 110/70. The picture of shock is not always commensurate with the amount of abdominal hemorrhage found at laparotomy. Three of the patients in this study were admitted in shock, but were

found, at laporatomy, to have *an unruptured tubal pregnancy,* and only a small amount of blood-tinged peritoneal fluid was present in the abdomen.

A gentle pelvic examination is preferred, but we find this difficult since most of our patients have marked abdominal and pelvic tenderness, and thus a gentle yet thorough pelvic examination is difficult to perform. A pelvic mass was found in 49 cases, or 36 per cent, but the chief finding was *tenderness in the cul-de-sac,* and *tenderness on manipulation of the cervix,* and to us, therefore, this tenderness appears to be the important diagnostic finding on pelvic examination.

The differential diagnosis between ectopic pregnancy and some other disease of the genital tract frequently may be difficult, and we have found centesis of the cul-de-sac to be a very helpful diagnostic aid. Needle aspiration of the cul-de-sac through the vaginal vault was performed in 129 of the 136 patients in our series, and in 123 cases the aspirated fluid was grossly bloody, the other 6 patients yielding only a very small amount of clear or cloudy peritoneal fluid. We consider not only the fact that blood is thus obtained, but that it does not coagulate, and that there are present some minute blood clots which are considered as diagnostic of hemorrhage into the peritoneal cavity. If one must resort to an animal pregnancy test for diagnosis, then the tubal pregnancy is probably not ruptured. We obtained a catheterized urine specimen from 11 women suspected of having ruptured ectopic pregnancy at the time of admission to the hospital, all of whom had immediate laparotomy. The Friedman test was positive in 10 of these cases and negative in one. All of the patients but one had ruptured ectopic pregnancies; this one woman had an unruptured tubal pregnancy and her test was positive.

Treatment

The main effort of treatment is control of the internal hemorrhage and blood replacement therapy. A delay in surgery is a major factor in the mortality rate, thus all of our patients are operated on as soon as possible, usually in one hour or less. Preoperative transfusions are used freely and result in the patient reaching the operating room in an improved or maintained state, and thus she is able to withstand the shock of anesthesia and laparotomy much better. Our anesthesiologists start the anesthesia as soon as the patient's blood pressure has risen to any level which would make general inhalation anesthesia feasible and safe. If the blood pressure cannot readily be brought up by blood transfusion we operate at once, using a rapid injection of local anesthetic, while other physicians are pumping in the blood.

The procedure most commonly performed is a unilateral salpingectomy followed by a modified Coffey suspension of the uterus. This was the treatment in 100 cases, while bilateral salpingectomy for quiescent pelvic inflammatory disease was done in 6 cases. A unilateral salpingo-oophorectomy was done in 22 cases and bilateral salpingo-oophorectomy in one case. Fundectomy was necessary in the three cases of interstitial pregnancy. An evacuation of the pregnancy and salpingostomy were done on the affected, remaining tube in 4 women who had had a previous tubal pregnancy and salpingectomy, and who desired children. This procedure, it is true, increases the chances of a third tubal pregnancy, but the patients were made cognizant of this fact prior to operation and still requested salvage of the remaining tube if possible. It is of interest to note that the Fallopian tubes originally removed in these 4 cases, on pathologic study, were found to be normal except for the tubal pregnancy. The pregnancy was found in the left salpinx in 64 cases, and in the right salpinx in 72 cases. In the 8 cases in which this was the second tubal pregnancy, the first tubal pregnancy had been in the left tube in 3 cases and in the right tube in 5 cases.

Additional elective surgery is very rarely warranted and, in our series, was done infrequently. Leiomyomas of the uterus were found in only 4 cases at time of surgery, and myomectomy was performed in only two of these. A repair of incisional hernia was done in one case, and colostomy and vaginal hysterectomy were each performed in one case. The hazard of appendectomy is too great to warrant its performance at the time of initial laparotomy for ruptured tubal pregnancy, and we do not do it.

All but 20 patients received blood transfusions prior to, during, and after surgery. We do not use plasma, which is less dangerous from the viewpoint of reactions, but with extensive internal hemorrhage adequate whole blood replacement therapy is mandatory, and although transfusion reactions may occur (and one of our fatalities was due to a transfusion reaction) we, nevertheless, continue the practice of using whole blood.

Pathology

The site of nidation of the ectopic pregnancy may be somewhat difficult to ascertain, but with the cooperation of the Department of Pathology, the site was determined by dividing the Fallopian tube into thirds. The results by this method are shown in Table III.

TABLE III. SITE OF NIDATION OF ECTOPIC PREGNANCY

	NO. OF CASES	PER CENT
Outer third	59	44
Middle third	46	34
Inner third	21	15
Interstitial	3	2
Secondary abdominal	5	4
Tubovarian	2	1
Total	136	

Pathologic study noted a ruptured tubal pregnancy in 124 cases, or 91 per cent, an unruptured tubal pregnancy in 5 cases, and a tubal abortion in the remaining 7 cases. A diagnosis of salpingitis was noted in only 37 cases, or 28 per cent, all except three of which patients were Negroes.

Postoperative Complications

At laparotomy no attempt was made to remove all the bloody fluid from the peritoneal cavity, and thus we expected an increase in morbidity beyond that of our regular laparotomies. According to the usual standards of morbidity, however, there were only 8 such cases. A few more patients, than in our regular experience, had a temperature rise the day of surgery, but this was not alarming, and antibiotic drugs were seldom used. We do not use antibiotic substances prophylactically in cases of extrauterine pregnancy. There were four patients who had postoperative complications: one patient had pyelitis, another thrombophlebitis, and a third had aspiration pneumonia (these three recovered during specific therapy). The fourth died of generalized peritonitis; she was cared for entirely on and by the surgical service.

Fatalities

There were four deaths in this series, a gross fatality rate of 2.9 per cent, and these are analyzed as follows:

One patient died a few moments after arrival, in a terminal state, in the emergency room, and thus became a coroner's case. She delayed overlong in seeking medical care, and

thus we feel that the patient was responsible for the outcome, for there was an interval (by history) of three days following onset of severe lower quadrant pain, and one day of marked syncope and weakness, during which she made no attempt to contact a physician. Had the patient sought medical care sooner she might well have survived.

The second death occurred in a patient on another service in our hospital. She was thought to have a malignancy of the sigmoid colon, which impression was substantiated by x-ray studies, but laparotomy disclosed, instead, that an old ectopic pregnancy had perforated the sigmoid. Although a colostomy was performed, the patient died of generalized peritonitis.

Anesthesia caused the third death. The patient had been carried along on cyclopropane during the laparotomy, and the anesthesiologist did not revert to nitrous oxide-oxygen and ether for the abdominal closure, merely discontinuing the cyclopropane at the conclusion of the operation. The patient died a few minutes after the anesthetic mask was removed, despite which event she had not been in shock before or during the laparotomy. This was adjudged a straightforward anesthesia death by the Department of Anesthesiology.

The fourth death was from acute renal insufficiency, the result of a blood transfusion reaction. The patient was inadvertently given the wrong type of citrated whole blood during the operative procedure and died of uremia seven days later, despite our efforts at management of her anuric state. The total amount of blood administered was 500 c.c.

From the above it is concluded that the gross fatality rate can be corrected from 2.9 per cent to 0.8 per cent for this series of cases, the one death ultimately ascribed to ectopic pregnancy being that in which the sigmoid had been perforated.

Comment

Certain causal factors are regularly discussed in any study of fatal cases of ectopic pregnancy. How to solve the problem of educating patients to seek medical care before they are moribund is not in the realm of this discussion.

The "delay in surgery" factor is usually the responsibility of the surgeon, and those willing to procrastinate and to adopt the policy of "wait and see" will always increase the risk to the patient. Internal hemorrhage calls for an emergency procedure. In any type of intra-abdominal hemorrhage the policy must be one of haste, and this is particularly true in cases of ruptured extrauterine pregnancy.

Laparotomy should be started as rapidly as possible following the making of a diagnosis, and this is likewise true in cases of secondary abdominal pregnancy. Very few patients die at the time of the original rupture, except those with interstitial (cornual) tubal pregnancy. Delay in aggressive operative measures permits further internal hemorrhage, and a resultant rise in morbidity and mortality.

The ovary of the affected side should and usually can be preserved. Occasionally there are some light periovarian adhesions, and the release of them may involve a few moments more, but this delay is well worth while since the preservation of the ovary, with an intact blood supply, must be accomplished. A tendency toward repeated tubal pregnancy is always present so long as one tube remains, and, if an ovary is removed each time salpingectomy is done, a young woman may be unnecessarily castrated.

The anesthesia for surgery, in our hospital, is entirely the responsibility of the members of the Department of Anesthesiology, but most of the operations in this series were done under inhalation anesthesia, it being preferred over spinal anesthesia in a patient already hyoptensive or potentially a candidate for

hypotension. Local anesthesia is excellent in moribund or badly shocked patients, but in the hands of a competent anesthesiologist our patients have done extremely well under general inhalation anesthesia, and our experience leads us to conclude that this is the best anesthesia in these cases.

We have attempted, by the use of needle aspiration of the cul-de-sac in any case in which extrauterine pregnancy is suspected, to minimize failure to diagnose the condition, and this has been a very successful procedure. We do not feel that pregnancy tests, curettage, or even the hemochromogen test are as positive aids in diagnosis as centesis of the cul-de-sac, and we believe the most valuable single aid in diagnosis is a properly executed aspiration of the cul-de-sac. This is also the belief of Collins and co-workers.[10]

Uterine curettage, as an aid in diagnosis in cases of ectopic pregnancy, has been of no benefit to us since one may obtain endometrium which shows any phase of a normal menstrual cycle and only occasionally will a decidual reaction be present. The variability of the phase of the endometrium in tubal pregnancy has been well presented by Romney and associates,[11] and bears out our feeling as to the uselessness of curettage in a case of suspected ectopic pregnancy.

Posterior colpotomy has not been done in any case since we prefer the abdominal route for treatment of suspected tubal pregnancy. If we are in doubt, but are reasonably suspicious that ectopic pregnancy is present, we perform an exploratory laparotomy.

We believe that a careful history, a gentle yet thorough pelvic examination, and an attitude in which one remains "ectopic pregnancy conscious" are necessary. When these are combined with carefully performed centesis of the cul-de-sac, proper diagnosis, in our hands, has not been difficult.

The fact of previous laparotomy has received considerable attention as a cause of ectopic pregnancy, but only 14 of our patients had had previous laparotomy, an incidence of 10 per cent, and 8 of these were for previous extrauterine pregnancy. Palpable or visible leiomyomas are described as having been found in only 4 cases, which is surprising considering that 84 per cent of our patients were Negroes. Adnexal masses were present in only those cases of salpingitis in which there was hydrosalpinx of the opposite tube.

At the time of rupture of a tubal pregnancy and separation of the trophoblastic tissue, it might be hypothecated that there exist the anatomic circumstances of a miniature abruptio placentae. If this be true, then defibrination of the blood is a possibility. It was difficult to find, among our patients, those suitable for a quantitative study of fibrinogen, fibrinolysin, or accelerator globulin. A delay of several hours following tubal rupture will permit the obtaining of blood samples unsuitable for study, for in such cases the clotting mechanism, had it been deranged at the onset, would most probably have seemed deranged by that time due to progressive deterioration of the "stagnant" blood.

In cases of ruptured ectopic pregnancy of less than six hours' duration, we found, in tests on 5 cases, that the venous blood fibrinogen was within the normal range, but, as might be expected, the fluid blood obtained from the abdomen at the time of laparotomy in 5 cases contained no fibrinogen, or, at best, a small amount. There was likewise no accelerator globulin in the fluid blood obtained

from the abdomen in the 5 cases so tested. The fluid blood obtained from the selected cases did not coagulate even after the addition of thrombin; thus, although these fluid blood samples seemed to be whole blood, it was nevertheless blood which had been clotted.

Mengert[14] noted that, after the introduction of uncitrated whole blood into the peritoneal cavity of selected gynecologic patients, most of the blood seemed to remain uncoagulated twenty-four hours after its introduction as determined at the time of laparotomy. Why? The mechanism of defibrination of blood in the peritoneal cavity is similar to that of taking whole uncitrated blood in the laboratory and bringing about defibrination by mechanical agitation. The constant activity of the intestinal tract, changes in postures, and bodily activities can easily be imagined to bring about this defibrination of blood in the abdominal cavity.

It is possible that the rupture and separation of trophoblastic tissue might cause alteration in the blood fibrinogen in interstitial pregnancies which usually remain in situ for 14 to 18 weeks or in cases of secondary abdominal pregnancy and sudden separation of the placenta from the pelvic viscera.

Summary

1. A study of 136 consecutive tubal pregnancies which occurred in a 30 month period is presented. The racial incidence was 84.5 per cent Negro and 15.5 per cent Caucasian. The ratio of ectopic pregnancy to term pregnancy in our clinic was 1:56 in Negroes, and 1:88 in Caucasians.

2. There were four fatalities, a gross rate of 2.9 per cent, which is correctable to a fatality rate of 0.8 per cent.

3. The factors contributing to mortality in tubal pregnancy are: (1) failure of diagnosis; (2) delay in surgery; (3) inadequate blood replacement; (4) elective surgery beyond the immediate need; (5) the patient's delay in seeking care.

4. Sterility was a common factor; 54 per cent of the patients in the study had been sterile for over four years.

5. Pelvic inflammatory disease was proved by pathologic study in only 28 per cent of the cases. We believe that salpingitis, although an important proved cause of tubal pregnancy, today appears to play a less prominent role in the etiology, and this point needs to be somewhat clarified in our teachings.

6. The history, gentle yet thorough pelvic examination, and an "ectopic pregnancy conscious" attitude, when combined with centesis of the cul-de-sac, will usually permit the ready diagnosis of extrauterine pregnancy. The most important diagnostic finding at time of pelvic examination, in our hands, is *tenderness* on manipulation of the cervix. The most valuable aid in diagnosis for us has been aspiration of the cul-de-sac with a 17 gauge needle. This was positive in 95 per cent of the cases of this study.

7. Only essential surgery should be performed in patients with tubal pregnancy, and salpingectomy should be done so as to spare the adjacent ovary with its blood supply intact in every possible instance. Appendectomy at the time of laparotomy for ectopic pregnancy is an inadvisable surgical procedure.

8. The postulation that defibrination of circulating blood might occur in ruptured tubal pregnancy is suggested. In the few cases in which we made tests, the circulating blood fibrinogen levels were within normal range, but no fibrinogen nor accelerator globulin was found in the fluid blood obtained from the abdomen at the time of laparotomy in the five cases so studied.

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A STUDY OF TWO HUNDRED FORTY-FIVE CASES OF RUPTURED ECTOPIC PREGNANCY*

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SINCE the beginning of human conception, one of the most dramatic episodes is the diagnosis and treatment of ectopic pregnancy. To date, notwithstanding all the studies on the subject, there is as yet no pathognomonic sign or symptom for the diagnosis of ectopic pregnancy. The diagnosis rests on a good clinical history, associated with the physical findings, and some laboratory tests, together with an "ectopic minded" medical man.

Many discussions of statistical data on ectopic pregnancy are confusing because they do not compare similar types of cases and their treatment. In some cases the diagnosis is apparent from the beginning; in others it is made by a process of exclusion.

There are two distinct groupings of cases of ectopic pregnancy: (1) the acute manifest cases with signs of internal hemorrhage; (2) obscure cases in which the products of conception and hemorrhage are walled off. This group of 245 cases will be so divided and discussed. Table I shows that 64 per cent of the cases are in the manifest group, and 94.6 per cent have a correct preoperative diagnosis; 36 per cent are in the obscure group, but only 76 per cent have a correct diagnosis.

TABLE I. TWO HUNDRED AND FORTY-FIVE CASES OF RUPTURED ECTOPIC PREGNANCY

GROUP	CLINICAL CLASSIFICATION	CASES	PERCENTAGE
I	Acute manifest cases with signs of internal hemorrhage	156	64.0
II	Obscure latent cases in which the products of conception and hemorrhage are walled off.	89	36.0
	Total	245	100.0

Material

This group of 245 cases comprises the cases of ectopic pregnancy treated in the Louisville General Hospital from July 1, 1927, to July 1, 1951, twenty-four consecutive years. Fig. 1 gives the incidence by years, and shows that there has been a progressive increase in the number of deliveries as well as cases of ectopic pregnancy. This is in accordance with the rise in births and increase in the population of the city. In this period of twenty-four years, there have been 31,010 live births recorded in the hospital, giving a ratio of one ectopic pregnancy to 126.5 births (Fig. 1). In this chart there are three distinct peaks—1933, 1940, 1947—the cause of which is not apparent, for they do not fluctuate with the number of live births. This may be a mute reminder of the astuteness of different residents.

*Presented to the Louisville Obstetrical and Gynecological Society, April 28, 1952.

In the past ten years there have been 2,595 major gynecological operative procedures in the General Hospital, an average of 260 major operations per year. The ratio is one ectopic pregnancy to 20 major gynecological operations.

Each of these cases of ectopic pregnancy has been confirmed by pathological reports of the specimen removed. There were 27 additional cases that were not confirmed and have not been included in this series.

Most patients with ectopic pregnancy are hospitalized. A majority of the abortions and deliveries are cared for in the homes, so a true ratio of ectopic pregnancies to normal pregnancies and abortions cannot be obtained. The calculated number of ectopic pregnancies throughout the country is in excess of 21,000 annually. The frequency calculated on the basis of live births is more accurate than when estimated on the basis of total pregnancies, because abortions can only be estimated. This is a vital factor in fetal and maternal deaths, and we should see that our vital statistics include cases of abortions and ectopic pregnancies.

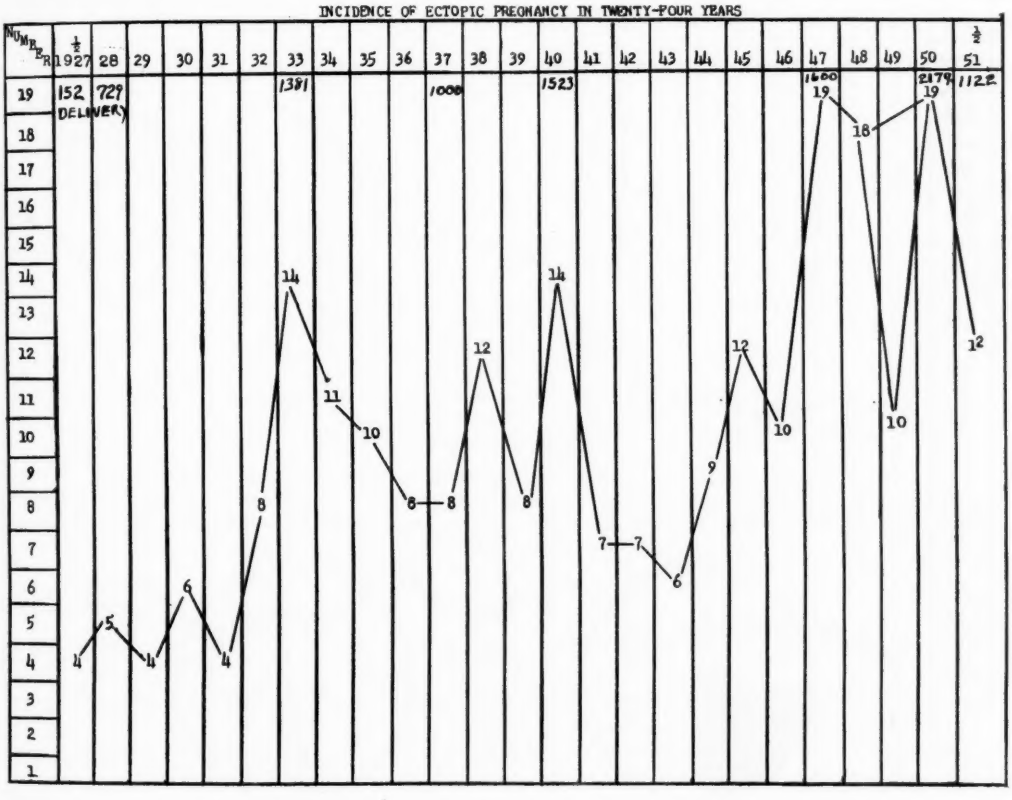


Fig. 1.

Infections still seem to be the predominant factor in causing ectopic pregnancy, but can one not expect an increase in ectopic pregnancies as a result of indiscriminate use of antibiotics and other drugs in the treatment of venereal infections? In this series 28 per cent had a definite history of infection; 52 per cent of the patients were Negroes; 11.5 per cent had a history of a positive Wassermann test (two-thirds of these were Negro patients). One would expect a greater increase of ectopic pregnancies in the Negro race, but this is not a conclusive finding in this series.

We find chronic salpingitis reported in 14 per cent of the acute cases, and in 37 per cent of the latent cases. In this series of 245 cases, 51 per cent had a pathological report of chronic salpingitis.

Over the period of twenty-four years we find a progressive increase in the number of ectopic pregnancies and the trend is in proportion to the population increase. A fifteen-year study of three private hospitals does not bear this out, but we have the following findings (Fig 2): In the Kentucky Baptist Hospital there was an annual average of 9 ectopic pregnancies; in Norton Memorial Infirmary, an average of 3.5; in St. Joseph's Infirmary, an average of 14. There has been a progressive rise from over 400 to 2,300 deliveries, but there has not been a proportionate increase in ectopic pregnancies in private hospitals. These private hospitals draw from the surrounding counties, while the General Hospital has only indigent patients from Jefferson County.

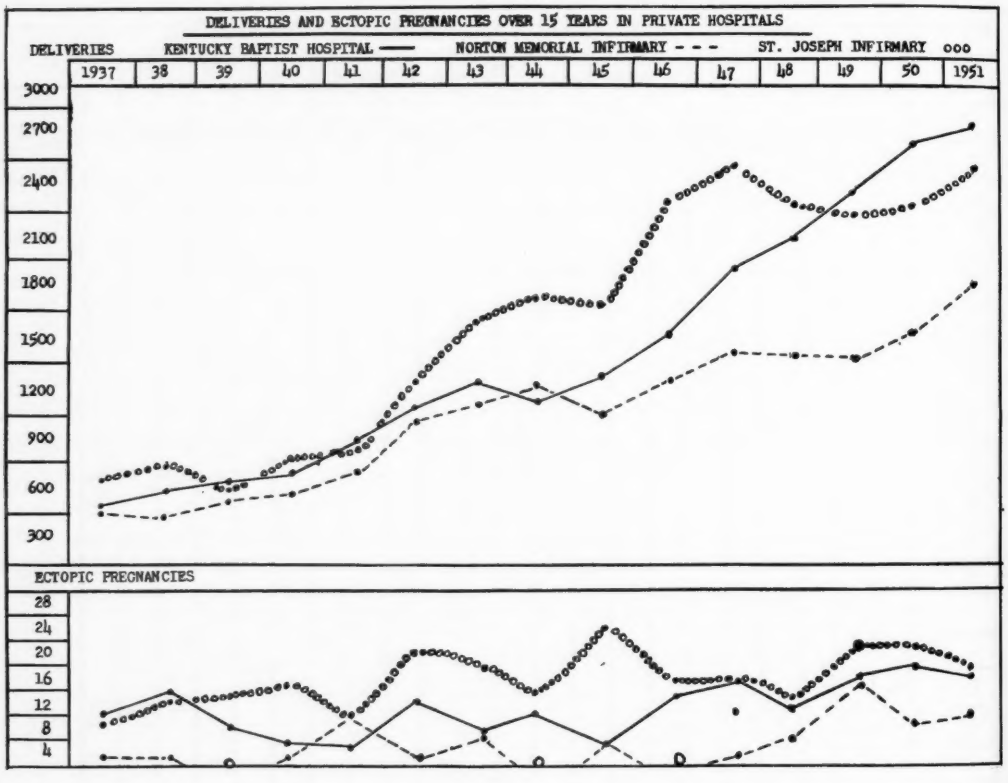


Fig. 2.

If we refer to the age groupings we find the highest peak between 20 and 30 years, and over 94 per cent of the cases occur between 20 and 40 years of age, which corresponds to the period of childbearing (Fig. 3). There is no real difference in this series between Negro and white age groups.

The chief symptoms were: (1) pain, (2) vaginal bleeding, (3) abdominal tenderness, and (4) rectal pain (Fig. 4).

Practically all patients at some time or other complain of pain. This may be present for only a day and be very sharp, but in most cases it is recurrent and continues as a dull, dragging ache in the lower abdomen. The rupture and its resulting effects are followed by nausea, vomiting, and continued bleeding.

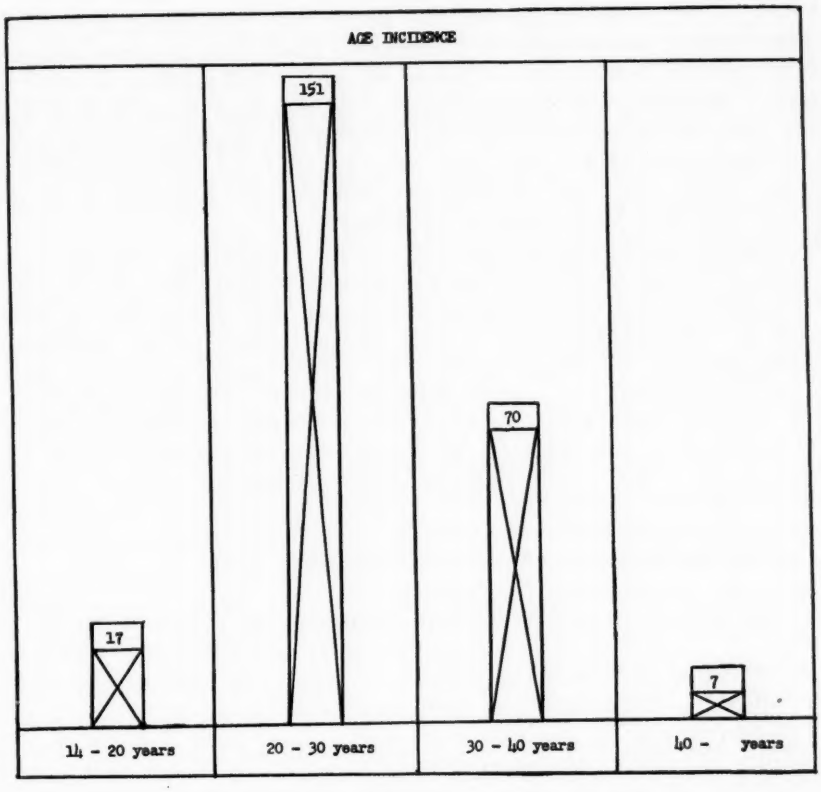
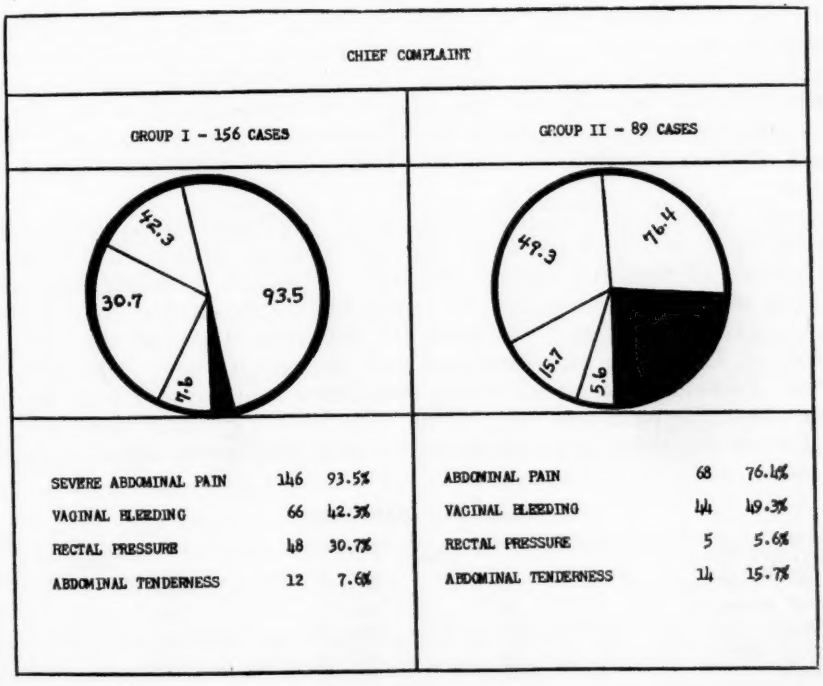


Fig. 3.



GROUP I - 156 CASES			GROUP II - 89 CASES		
SEVERE ABDOMINAL PAIN	146	93.5%	ABDOMINAL PAIN	68	76.4%
VAGINAL BLEEDING	66	42.3%	VAGINAL BLEEDING	44	49.3%
RECTAL PRESSURE	48	30.7%	RECTAL PRESSURE	5	5.6%
ABDOMINAL TENDERNESS	12	7.6%	ABDOMINAL TENDERNESS	14	15.7%

Fig. 4.

We find in the manifest group that acute pain is present in 93.5 per cent of the cases, and in 54 per cent of these cases there was an acute onset of pain in less than twenty-four hours. Vaginal bleeding was present in 42.3 per cent of the cases. Bleeding was less profuse in the manifest cases than in the latent cases. The association of the symptoms of recurrent attacks of pain and vaginal bleeding is most important. The types of associated symptoms are more acute in the manifest cases. We can readily see that vaginal bleeding is present as a complaint in less than 50 per cent of these cases.

The average age in this series is 27 years. In Group I 16 per cent of the patients had abortions shortly before the ectopic pregnancies; 17 of the ectopic pregnancies were in the first pregnancies, and a high percentage of these cases were in the second decade of life. Most of these were in the manifest group. The youngest patient was 14 years old; the oldest was 43. The average age in the acute manifest group was 7 years younger than in the latent group. Of these patients 80 per cent were multiparous, with an average of 2.9 children per marriage. Five patients were married twice with ectopic pregnancies in both marriages, and 11 per cent of the patients were unmarried. There were 2 cases of ectopic pregnancy in one horn and normal pregnancy in the uterus, which aborted later. There was one patient with a ruptured ectopic pregnancy in one tube and an unruptured pregnancy in the opposite tube.

The average time between the previous gestation and ectopic pregnancy was 5.2 years. There were 2 patients with an eighteen-year interval; 3 patients with a twelve-year interval; 3 with an eleven-year interval; 2 with a ten-year interval. What was the cause of these long periods of infertility—infections, inadequate glandular function, contraceptives, general disability in one or both parties?

Over 86 per cent of the patients were said to have normal menstrual periods. Some indefinite periods of amenorrhea were reported in 26 per cent of the cases. Cholocate-colored vaginal bleeding or spotting is a valuable sign in these cases. On careful study of these cases one might have found that the last regular period was either abnormally short and scant or delayed. But to get an accurate picture of the menstrual cycle, especially in Negro women, is most difficult. It is nevertheless important in deciding the diagnosis. The average duration of amenorrhea in the series was 2.4 months. The length of time from the last menstrual period to the time of the operation in both the manifest and the latent ectopic pregnancies falls well within an eight- to twelve-week period. The longest period of time occurred in 2 of the abdominal pregnancies and was over six months.

No type of bleeding was common in either the manifest or the latent cases, but 28.6 per cent of the manifest group and 11.2 per cent of the latent group gave no history of bleeding before operation. Vaginal bleeding does occur in about 50 per cent of the cases, and is a valuable symptom, but pain is the most constant symptom; likewise it varies in the different stages of the condition as to its severity, intensity, and location, and, unless properly interpreted, it is misleading. In over 94 per cent of the manifest cases and about 50 per cent of the latent cases the pain was cramplike. In the very acute cases with shock, pain in the left shoulder and the desire to stool (bathroom sign) is present in

TABLE II. SYMPTOMS

SYMPTOMS	GROUP I		GROUP II	
Nausea and Vomiting	82	52.5%	43	48.5%
Fainting and weakness	72	46.0%	36	40.4%
Missed periods	62	39.7%	5	5.5%
Pressure in rectum	48	30.7%	5	5.5%
Shoulder pain	31	19.8%	3	3.3%
Dysuria and frequency	24	15.3%	15	16.0%
Breast changes	17	10.8%	14	15.6%

over 18 per cent of the cases, and is of greatest significance. Abdominal tenderness and rebound pain are of importance in both groups. In 52.5 per cent of the manifest cases there was a shifting dullness. Nausea, vomiting, and urinary frequency occurred in over 15.3 per cent of the acute cases, and was present to a lesser degree in the latent cases. The symptoms of the two groups of cases are compared in Table II.

The laboratory findings (Table III) show a secondary anemia in manifest cases with a leukocytosis, and 38.5 per cent of these had findings of under 60 per cent hemoglobin. But the difference in the counts is of great importance. A sudden fall in hemoglobin and count without much change in the clinical picture is of great importance. The total red blood count is the most important part of the blood picture in ectopic pregnancy. The anemia alone is not the cause of shock. Some patients with a count of 2,500,000 have no shock, while others with 3,500,000 are in shock. In the latent cases the counts were about normal as an average. Urine examinations in most instances were normal.

TABLE III. COMBINED LABORATORY DATA

	RED BLOOD COUNT	WHITE BLOOD COUNT	HEMO-GLOBIN	KAHN TEST	ASCHHEIM-ZONDEK TEST, ETC.	BLOOD PRESSURE	TEMP.
Group I.–	3,559,000 (Average)	12,562 (Average)	9.6 (Average)	23 positive	46 cases 19 positive	30/0 to 112/62	96.0° to 100.6°
Group II.–	4,027,000	7,281	10.8	6 positive	Negative	118/78 (Average)	99.2° (Average)

The admission pulse, temperature, and blood pressure are important. In the manifest cases there was a rise of 20 points in the pulse rate, with an average fall of more than 30 points in systolic blood pressure. Over 33 per cent of the manifest cases had subnormal temperature and were in shock on admission. Tenderness on moving the cervix, a soft cervix, slightly enlarged uterus, with a unilateral adnexal mass or tenderness and a cul-de-sac bulging or tenderness, form a most conclusive group of symptoms (Table IV). Add to this blood from a cul-de-sac puncture and the diagnosis of ectopic pregnancy is practically confirmed. The combination of a careful clinical history and physical findings by an "ectopic minded" medical man is very important.

TABLE IV. CLINICAL FINDINGS

	GROUP I		GROUP II	
Abdominal Findings.—				
Tenderness	75	48.0%	29	31.4%
Rigidity	28	17.0%	5	5.5%
Distention	25	16.0%	10	11.1%
Fluid	23	14.7%	10	11.1%
Muscle spasm	22	14.0%		
Pelvic Findings.—				
Palpable mass	116	74.3%	72	82.7%
Soft cervix	91	58.0%	36	40.4%
Pain on manipulation	73	46.7%	35	39.0%
Enlarged uterus	57	36.5%	42	47.0%
Extreme pelvic tenderness	40	25.0%	8	9.0%
Bulging cul-de-sac	33	21.0%	3	3.3%
Abdominal pregnancy			7	7.8%

Our attitude toward the Aschheim-Zondek tests is that they are of little importance. A positive delayed direct van den Bergh test is of help in that it may indicate the presence of free blood in the peritoneal cavity. Posterior colpotomy with aspiration of cul-de-sac bloody fluid is one of the simplest diag-

nostic aids, and is reliable in over 96 per cent of the cases (Table V). It is relatively simple and fairly safe, and should be done in every case in which ectopic pregnancy is suspected. This can be done in either the accident ward or the operating room. Sedimentation rates are helpful in differentiating between pelvic inflammation and ectopic pregnancy in the latent cases, but are of little significance in the manifest cases.

TABLE V

	COLPOTOMY	AVERAGE INTERVAL FROM ADMISSION TIME TO OPERATING ROOM	AVERAGE TIME IN SURGERY	ABDOMINAL BLOOD	ADDITIONAL SURGERY	ANESTHESIA
Group I.—	43 done 38 positive	3 hours, 35 minutes	52 minutes	98 %	86% tube only 12% tube, ovary, appendix	94% general 6% spinal
Group II.—	24 done 19 positive	3 days	82 minutes	53.7% (free) 46.0% (walled off)	37% tube only 26% tube, ovary 27% bilateral tube 38% appendix 21% hysterectomy	64% general 36% spinal

The average time from admission to the hospital to the time of operation in the manifest cases was 3 hours, 35 minutes. This ranged from 20 minutes to 9 hours, 45 minutes. In the obscure cases the average time from admission to the hospital to the time of operation was 3 days. Some of the cases were treated for three weeks. The average operation time in the latent cases was 1 hour, 20 minutes. In the acute manifest cases 55 minutes was the average time required for completion of the operation. The average hospital days were seven, with the latent cases most prolonged.

In 98 per cent of the manifest cases there was free blood in the abdominal cavity, but in the obscure cases about one-half had the blood and products of ectopic pregnancy walled off. Cullen's sign, a bluish discoloration about the umbilicus, is a textbook curiosity, and is only occasionally found.

In 86 per cent of the manifest cases only a salpingectomy was done, together with removal of the free blood from the peritoneal cavity. In the obscure (27%) cases, 37 per cent had single tubes removed, and bilateral salpingectomies were done; 26 per cent had a tube and ovary removed, and 38 per cent of the patients had appendectomies at the same time. Most of these were in the obscure cases. I believe that the removal of the appendix in manifest cases is unwarranted and is meddling surgery. In the obscure cases 21 per cent had hysterectomies, and these were justified. This is one reason why the two groups cannot be compared without undue criticism and misunderstanding, both as to the extent of surgery and to mortality.

The type of anesthesia used has been of interest. In the acute cases practically all were given some form of general anesthesia; nitrous oxide alone or cyclopropane, nitrous oxide and ether, Pentothal and ether, or Pentothal and curare. Only 6 per cent were given spinal anesthesia and this was with great caution. Some of these patients were in shock and only a local anesthetic was necessary. We feel that spinal anesthesia adds greatly to shock from hemorrhage and therefore a general anesthetic with a high percentage of oxygen is preferred.

In 64 per cent of the latent cases general anesthesia was given. Pentothal and spinal anesthesia were used in 36 per cent of the cases. We feel that general anesthesia is superior and is controlled better in these very critical states, and in acute cases it is the anesthesia of choice.

The development and ease of blood transfusions have caused them, of all the procedures, to play the greatest part in the reduction of mortality and it is of interest to note the change in treatment. From 1927 to 1941 we gave transfusions and autohemotransfusions in 27 per cent of the manifest cases, and in 24 per cent of the latent cases. The mortality was 3.6 per cent. From 1946 to 1951 we have not had a death from ectopic pregnancy, and this is in a great measure due to the giving of early, frequent, and adequate transfusions (Table VI). However, blood transfusions can never replace the necessity of ligating the bleeding artery. One can say that the mortality in ectopic pregnancy is, for the most part, from neglect.

TABLE VI. FOLLOW-UP

TRANSFUSIONS	PATHOLOGY			MORTALITY	FOLLOW-UP
Group I.—					
41% had 500 c.c. or over whole blood transfusion, during or after operation	Ruptured ectopic pregnancy		156	1 died 4 days postoperatively of pneumonia	77% well with no complaints 2 weeks to 2 years
	Right	59.6%			
	Left	30.7%			
	Bilateral	9.6%		1 died of transfusion reaction and uremia	
17.3% had autohemotransfusion	Chronic salpingitis	14%		1 died of shock and hemorrhage	8% had symptoms—dysmenorrhea, vaginal discharge, pyelitis, pelvic pain
	Ovarian cyst (retention)	9%			
	Appendectomy (incidental)	3%			
Group II.—					
22% had 500 c.c. or over whole blood transfusion during the operation	Ruptured ectopic pregnancy		89	1 case of heart failure	
	Right	45.9%			
	Left	28.2%		1 died of peritonitis 10 days postoperatively	
	Bilateral	25.8%			
No autohemotransfusion	Chronic salpingitis	37%		1 died of concealed hemorrhage	15% no follow-up
	Ovarian cyst (retention)	28%			
	Appendectomy (incidental)	38%		Total deaths 6	
				Mortality 2.4%	
	Fibroids	12%			
	Ovarian pregnancy	1 case			
	Abdominal pregnancy	7 cases			

In the 245 cases in twenty-four years there were 6 deaths, or a mortality rate of 2.4 per cent, without a death in the last six years. This is clearly due to "ectopic minded" doctors who operate earlier and transfuse adequately.

The follow-up shows that 77 per cent of the patients have no complaints after two weeks to two years, and quite a few have had normal pregnancies afterward. About 8 per cent have complaints of dyspareunia, pelvic pressure, vaginal discharge, rectal pressure, and irregularity of periods. About 15 per cent did not return for the follow-up and cannot be reported as to results.

Some of the unusual findings were: (1) one authentic ovarian pregnancy (there are only 121 cases of authentic ovarian pregnancy reported in literature as of September, 1951); (2) seven secondary abdominal pregnancies, none of which were viable, or delivered a living child (they were between 3 and 6 months old and were definitely attached to the abdominal structures); (3) two cases of ectopic pregnancy and uterine pregnancy; (4) one case of ectopic

pregnancy in both tubes, one unruptured; (5) five patients had two marriages with ectopic pregnancies in both marriages; (6) seventeen cases were first pregnancies. Of these cases, 11 were in unmarried women.

Retention cystic changes in the ovaries was found in 28 per cent of the latent cases. As to the diagnosis of ectopic pregnancy, the failure to find decidua does not rule out an existing ectopic pregnancy. Decidua without chorionic villi have been shown to be present in 20 per cent of the cases; in 40 per cent there is secretory endometrium; in 30 per cent proliferative endometrium; and menstrual endometrium in only 6 per cent. Therefore the endometrial findings are not conclusive.

Summary

A review is given of 245 cases of ruptured ectopic pregnancy in one institution in twenty-four years, presenting a classification to aid discussion of the findings, and stressing the importance of "ectopic minded" medical men, in every case where a woman of childbearing age presents a diagnostic problem in the lower abdomen. Early ligation of the bleeding artery and adequate replacement of blood are the immediate responsibilities of the surgeon.

The mortality in ectopic pregnancies is usually the result of neglect or procrastination. The mortality rate was 2.4 per cent.

Some unusual cases in this series were mentioned.

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THE TREATMENT OF FUNCTIONAL AMENORRHEA*

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AMENORRHEA is a symptom of endocrine imbalance. Disturbances of physiology, rather than pathologic lesions, are responsible for its occurrence in most instances. In fact, disturbances of menstruation are so common to practically all types of major endocrine disorders that a regular ovulatory menstrual cycle is presumptive evidence of pituitary-ovarian equilibrium. Ovulatory menstruation is the end point of a balanced series of physiologic events involving a dynamic relationship between the anterior pituitary gland, the ovary, and the endometrium. The thyroid and adrenal functions, as well as the general nutritional and emotional state, exert profound influence on cyclic reproductive function. These extragenital factors were lucidly demonstrated by Goldberg and Lisser[1] in their graphic classification of amenorrhea on the basis of organ level of origin. Amenorrhea may result from alteration of the normal physiology at any link in the chain of events which influences maturation of the endometrium to the pregravid state and its subsequent shedding. For this reason, systematic thinking in terms of physiologic mechanisms is essential in clinical evaluation of the patient.

Types of Amenorrhea

Since amenorrhea is a symptom of endocrine dysfunction with a variety of causes, many complex methods of classification have been offered. Clinical application of most of these is impractical. Traditionally, the condition has been divided into two main types, depending upon whether or not the patient has previously experienced menstrual bleeding. The number of subtypes is legion. The adult woman who has never menstruated is said to have *primary* amenorrhea. Amenorrhea is *secondary* when a woman of childbearing age gives a history of having menstruated more or less regularly in the past, but has had no signs of catamenia for some time—which may be arbitrarily placed at one or more years. Amenorrhea is said to be *functional* when menses occur irregularly at intervals of three to nine months or longer, and *physiologic* when associated with pregnancy, lactation, or the menopause. With the exception of those cases involving end-organ failure, such as nonresponsiveness of the endometrium or congenital anomalies involving the uterus, amenorrhea may be further classified as hypohormonal or hyperhormonal.

Menstrual Physiology

Cerebral Factors.—The hypothalamus is the site of integration of activity of the central and autonomic nervous systems and profoundly influences the effect of the pituitary on the target glands of the endocrine system. The path-

*The oral estrogen and progesterone used in this study were supplied through the courtesy of Dr. H. F. Hallman, the Upjohn Company, Kalamazoo, Mich., as Urestrin (1 mg.) and progesterone (30 mg.) in tablet form. The anhydrohydroxyprogesterone used was Pranone (Schering) and Lutocylol (Ciba).

ologic physiology of psychogenic or hypothalamic factors resulting in amenorrhea was described by Reinfenstein in 1946.[2] He suggested that emotional trauma produced a block to the normal continuous impulses from the hypothalamus to the anterior pituitary for the release of luteinizing hormone. Amenorrhea associated with pseudocyesis or fear of pregnancy, maladjustment to changes in environment, disturbing emotional episodes, anorexia nervosa, and certain types of "war" amenorrhea[3] are included in this group (Fig. 1).

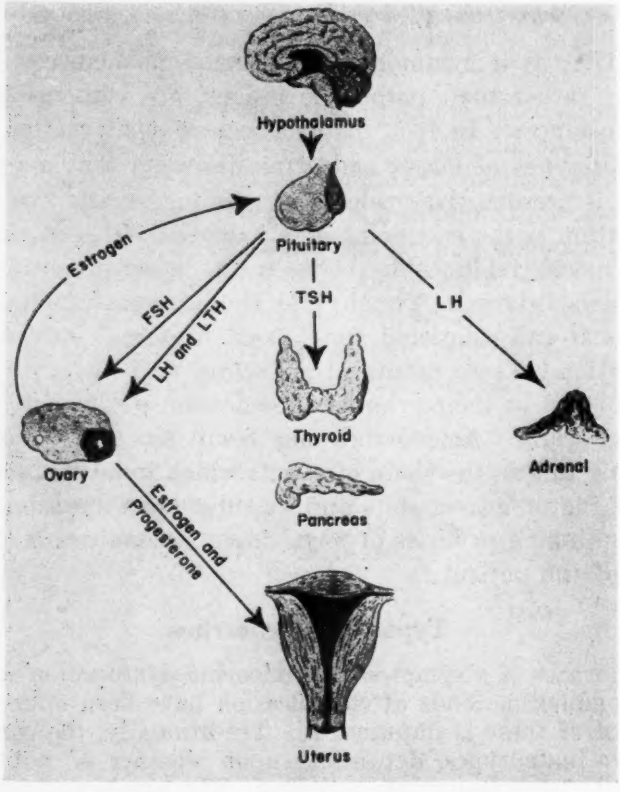

Fig. 1.—Possible organ level of origin for amenorrhea.

The Pituitary.—The pituitary gonadotropins are necessary in proper amounts for maturation of the Graafian follicle, ovulation, and maintenance of the corpus luteum. Amenorrhea of pituitary origin may result from primary lack of follicle-stimulating hormone (FSH), or normal FSH with deficient luteinizing hormone (LH). A third pituitary factor, the luteotrophic hormone, is necessary for maintenance of the corpus luteum. In amenorrhea of pituitary origin there is often some evidence of other glandular deficiency, such as disorders in statural growth, thyroid and adrenal insufficiency, sexual infantilism and scanty or complete absence of axillary and pubic hair. Urinary gonadotropin titers are useful in differentiating amenorrhea of pituitary and ovarian origin. A high titer rules out pituitary failure and implicates ovarian failure. Certain tumors of the pituitary which produce acromegaly and Cushing's disease may be considered hyperhormonal causes of amenorrhea. An x-ray of the sella turcica is frequently useful in establishing the presence of lesions of the pituitary.

The Ovaries.—For cyclic function, the ovaries must be capable of response to pituitary stimulation. Congenital absence or aplasia of the ovaries[4] results in primary amenorrhea associated with sexual infantilism, dwarfism, and lack

of breast development, and when these are associated with congenital anomalies, the condition is called Turner's syndrome.[5] The development of axillary and pubic hair depends on normal function of the ovaries, but is dependent also on normal pituitary and adrenal function. Ovarian estrogens, it is believed, stimulate the release of pituitary LH which causes adrenal production of androgens necessary for hair growth.[4] Ovarian function can best be studied by endometrial biopsy since the endometrium reflects the changes taking place in the ovary, and the occurrence or absence of ovulation can be determined with certainty. With proper technique this biopsy may be obtained as an office procedure by aspiration curettage. Study of the vaginal cytology with any simple office staining technique will reveal the presence or absence of adequate estrogen function. In the presence of apparently adequate estrogens, amenorrhea may result from failure of ovulation. This is by far the most common cause of functional amenorrhea. In absence of ovulation the endometrial biopsy reveals a persistent estrogenic phase, a proliferative phase, or, at times, hyperplasia of the cystic glandular type. Failure of ovulation may result from an inherent inability of the ovary to respond to pituitary gonadotropins, or from absence or imbalance of these hormones due to pituitary dysfunction, which may be primary or secondary to extrinsic factors. The syndrome of hirsutism and amenorrhea with large microcystic abiotrophic ovaries, in which estrogens are produced, but ovulation does not take place, may also be included in this group (Stein-Leventhal syndrome).[6] Tumors of the ovary which produce excessive estrogen or progesterone, and virilizing tumors such as arrhenoblastoma, are hyperhormonal causes of amenorrhea. Amenorrhea frequently follows control of functional uterine bleeding whether this is accomplished by curettage or by endocrine therapy,[7] since in many instances the abnormal bleeding, as well as the amenorrhea, is the result of failure of ovulation.

Endometrial Factors.—The end organ from which bleeding occurs must be capable of adequate response to the many factors which influence its cyclic preparation for nidation. Estrogens stimulate the proliferation of glands of the tubular type in the endometrium, and progesterone, along with increased amounts of estrogen from the corpus luteum, causes profound changes in the stroma, vascularity, and secretory changes in the glandular elements. Atrophic endometrium is indicative of estrogen deficiency, and a follicular endometrium or cystic glandular hyperplasia indicates the presence of estrogen but absence of ovulation. Amenorrhea resulting from failure of the endometrium to respond to adequate estrogen and progesterone stimulation is rare, although two cases of hormone-resistant psychogenic amenorrhea were recently reported by the Goldziehers.[8] Such factors as previous radiation therapy, overwhelming infection, or too-zealous curettage must be considered.

Factors Influencing the Menstrual Mechanism.—Adequate thyroid function is essential to normal pituitary and ovarian function. In cretinism, for instance, with total absence of thyroid function, there is lack of response to pituitary growth hormones, and the individual never matures and may never menstruate. Disturbances of ovarian function manifested by either menorrhagia or infrequent, scanty menstrual periods are observed in both hypothyroidism and hyperthyroidism. Menstrual disturbances are so frequently the result of mild thyroid deficiency that gratifying results of empiric thyroid therapy have been observed for many years in management of gynecic problems. Evaluation of the basal metabolism and blood cholesterol is an easily available means of evaluating thyroid function.

Amenorrhea is frequently seen in Addison's disease. Congenital cortical hyperplasia which produces excessive androgens in the female child results in female pseudohermaphroditism, and when hyperplasia or tumor develops later in life a syndrome of virilism with amenorrhea (adrenogenital syndrome) results. Amenorrhea is also observed in tumors of the glucocorticoid portion of

the adrenal cortex (Cushing's syndrome) or diffuse hyperplasia of this tissue (Cushing's disease).

Although the pancreas is not an integral factor in the reproductive mechanism, some patients with diabetes mellitus have episodes of functional amenorrhea.

Amenorrhea may be a physiologic means of conservation of vital blood when associated with starvation, severe anemia or chronic debilitating disease such as advanced tuberculosis. It may be a physiologic method of preventing the metabolic strain of reproduction under adverse circumstances. Be that as it may, treatment in these instances should obviously be directed toward the primary condition rather than the amenorrhea. Amenorrhea may also accompany or follow acute infectious diseases.

Diagnosis and General Measures in Treatment of Functional Amenorrhea

A complete history with effort to disclose any sources of emotional disturbance, and a thorough physical examination are essential. The general physical examination should include complete laboratory studies and a chest x-ray. The pelvic examination may reveal congenital anomalies or disease of the pelvic organs. Evaluation of the vaginal cytology will reveal the presence or absence of adequate estrogen stimulation. This may be accomplished very simply by staining a freshly prepared slide of the vaginal secretions with 1 per cent pinacyanol for 30 to 60 seconds[9] or by other standard procedures such as the Shorr stain or the Papanicolaou technique.

A majority of cornified or precornified epithelial cells with dense pyknotic nuclei is indicative of estrogen activity. On the other hand, if the cells are small and round, containing large nuclei, estrogen deficiency exists. An endometrial biopsy is of value in revealing the status of ovarian activity.

Management of Patient.—Before hormonal therapy for amenorrhea is instituted an attempt should be made to correct dietary deficiencies or excesses, as well as any environmental or psychological conflicts. When amenorrhea is associated with obesity, frequently weight reduction is all that is necessary for return of cyclic menses. If the fasting blood cholesterol is elevated or within the upper limits of normal, small doses of thyroid (one-half grain daily) for several months are of value. When a patient with irregular and infrequent menses is in good health otherwise, she should be reassured that her menstrual irregularity has no organic basis and encouraged not to worry about it. Estimation of the urinary gonadotropin titer will aid in differentiating primary ovarian failure from ovarian failure which is secondary to hypofunction of the anterior pituitary. Some patients with low gonadotropin levels respond well to cyclic courses of combined anterior pituitary extracts and chorionic gonadotropin after priming with estrogens.[10, 11] The use of gonadotropins, on the other hand, appears to be contraindicated when the endometrial biopsy persistently reveals hyperplastic endometrium,[12] and in these instances one may assume an imbalance in the pituitary-ovarian relationship. Patients with high urinary gonadotropin titers probably have normal pituitary function with inadequate ovarian response and the prognosis for spontaneous ovulation is poor.

To decide whether or not treatment for functional amenorrhea is indicated is a medical responsibility. Although treatment of the amenorrhea itself is not always necessary, adequate study of the individual case will frequently enable the physician to make an early diagnosis of serious organic disorders. Since periodic bleeding is a manifestation of normal reproductive function, many amenorrheic patients feel that they are abnormal and allow this to become a source of extreme emotional anxiety. In these individuals, a sense of well-being and health is imparted by cyclic induction of bleeding. Amenorrheic women

who desire children should be treated because treatment occasionally establishes better equilibrium between the pituitary and ovarian function, and if ovulation does occur—even though infrequently—the chances of conception are improved. Some patients, on the other hand, repeatedly develop cystic glandular hyperplasia of the endometrium with menorrhagia as a result of prolonged estrogen stimulation without the intermittent desquamative effect of progesterone withdrawal. In these patients repeated bouts of menorrhagia can be avoided by induction of cyclic bleeding with shedding of the endometrium. Frequently following the control of menorrhagia, whether by curettage or hormonal methods,[7] patients remain anovulatory for indefinite periods of time, as indicated by basal temperature records or endometrial biopsy, with recurrence of menorrhagia unless bleeding is induced. It becomes apparent then that a certain group of patients require treatment for functional amenorrhea. Since normal cyclic function is the result of alternate stimulation and inhibition of the various tissues involved in the ovulatory and menstrual mechanism, it appears that simulation of these natural influences is a rational approach to therapy, and offers an opportunity for establishment of improved spontaneous hormonal equilibrium. The success achieved by substitutional therapy probably is due to various contributing factors, of which priming the uterus, physiologic resting of the ovaries, and mediation of anterior pituitary function are the most important.[13]

Specific Treatment of Functional Amenorrhea.—Bleeding can be induced by adequate estrogen and progesterone stimulation in practically every patient with an intact uterus and endometrium, whether or not the ovaries are present.[14] Furthermore, when endometrial biopsy and vaginal cytology indicate that adequate intrinsic estrogens are present, withdrawal bleeding can be induced in practically every patient with an intact uterus and endometrium with progestin therapy alone. This may be administered as progesterone parenterally (10 mg. per day for three to five consecutive days), or orally (30 mg three times daily for five days), or as anhydrohydroxyprogesterone (10 mg. three times daily for five days) to produce "progesterone withdrawal bleeding."[15, 16] This bleeding usually begins 24 to 96 hours after completion of the above course of therapy. Occasionally, bleeding begins before therapy is completed, and this has been referred to as "breakthrough bleeding."[17] If therapy is started after spontaneous ovulation has occurred bleeding may be delayed 10 to 14 days.

When intrinsic estrogen levels are low as indicated by the study of the endometrium or vaginal cytology, progestin therapy alone is insufficient to produce bleeding. In such cases it is necessary to prime the endometrium first with estrogens. This may be accomplished by giving estrone sulfate, 1.25 mg. or its equivalent daily for 20 days, followed by a course of progestin therapy as outlined above. Although bleeding may occur after withdrawal of estrogen therapy when given alone, we prefer to follow this with progestin therapy because it more nearly simulates normal function, and the duration of bleeding is more constant and predictable.

Since progesterone is ineffective in the absence of adequate estrogens, the simultaneous administration of estrogen and progesterone was employed at this clinic and reported as early as 1939.[18] A systematized method was independently offered by Zondek in 1942 utilizing 5 mg. of estradiol benzoate and 25 mg. of progesterone in divided doses intramuscularly over a 2 day period.[19] In many patients with adequate intrinsic estrogens a single injection of estrogenic substances (2.5 mg.) and progesterone (25 mg.) was sufficient to produce bleeding within 24 to 72 hours. In some patients with severe psychic factors such as pseudocyesis or fear of pregnancy it may be necessary to prime the uterus with estrogens for 20 to 30 days before a course of parenteral estrogen (2.5 mg.) and progesterone (25 mg.) daily for five days will be sufficient to produce bleeding.

A Clinical Problem

The effectiveness of ingested anhydrohydroxyprogesterone has become well established. Since a clinical study at this clinic recently indicated that progesterone is also physiologically effective when ingested in adequate dosage,[16] the question arose as to whether simultaneous oral administration of estrogen would increase the effectiveness of the progesterone and/or avoid the necessity of estrogen priming in patients with estrogen deficiency.

Materials and Methods

Observations were made on 123 patients in 334 courses of progestin therapy for functional amenorrhea with an attempt to compare the effectiveness of anhydrohydroxyprogesterone, progesterone, and combined estrogen-progesterone when these drugs are ingested. The medication was in the form of tablets prepared for ingestion and containing (a) anhydrohydroxyprogesterone—10 mg., (b) progesterone—30 mg., or (c) estrogenic substances—1 mg. and progesterone —30 mg. The dosage used for each of the above preparations was one tablet three times daily for 5 consecutive days. Basal temperature records were kept by all patients and therapy was omitted when ovulation occurred.

Results

The number of patients observed and the results of therapy with each of these preparations are presented in Table I. Although pregnancy tests were performed whenever indicated, six courses of therapy with the estrogen-progesterone combination were not included in the statistical evaluation because basal body temperature records indicated that ovulation occurred during or immediately after the course of therapy and conception intervened. These same patients had responded to therapy in one or more preceding months without evidence of ovulation as indicated in the basal temperature record and/or endometrial biopsy. Similarly, during the course of cyclic therapy for several months, withdrawal bleeding was delayed in 10 to 14 days after completion of therapy in 22 instances, and the basal temperature record indicated that ovulation intervened and postponed the withdrawal bleeding. These instances were not regarded as therapeutic failures because recurrence of spontaneous ovulation is the aim and end point of therapy. The simultaneous administration of

TABLE I. FUNCTIONAL AMENORRHEA

ORAL THERAPY	TOTAL PATIENTS	COURSES OF THERAPY	BLEEDING FOLLOWED THERAPY	PER CENT EFFECTIVE
Anhydrohydroxyprogesterone 10 mg. t.i.d. 5 days	22	44	40	90.9 With adequate estrogenic smear
Progesterone 30 mg. t.i.d. 5 days	25	61	55	90.45 After estrogen priming (88.6) With adequate smear (92.3)
Estrogens and progesterone 1 mg. E. and 30 mg. P. t.i.d. 5 days	76	223*	210†	94.1

*Six additional courses not included because pregnancy intervened.

†In 22 courses bleeding was delayed 10 to 14 days because ovulation occurred during therapy or immediately thereafter.

estrogenic substances with the ingested progesterone in the dosage used over a 5-day period of oral therapy was not sufficient to take the place of estrogen priming for 20 to 30 days in those individuals who showed evidence of inadequate intrinsic estrogens. The use of these steroids in combination would appear more physiologic in replacement therapy than Progestin alone since, after all, the corpus luteum produces both estrogen and progesterone.

Summary

1. A method of approach to evaluation of the amenorrheic patient with emphasis on the importance of thinking in terms of physiologic processes in arriving at a differential diagnosis of cause is presented.

2. General measures, indications for therapy, and specific hormonal therapy which has been successfully employed in functional amenorrhea are discussed.

3. Results of clinical observations in 328 courses of therapy administered to 123 patients with functional amenorrhea employing either (a) anhydrohydroxyprogesterone—10 mg., (b) progesterone—30 mg., or (c) a combination of estrogenic substances—1 mg. and progesterone—30 mg., by ingestion, three times daily for 5 consecutive days are compared. These preparations were found to be equally effective by ingestion in the dosage used, and withdrawal bleeding followed therapy in (a) 90.9 per cent, (b) 90.45 per cent, and (c) 94.1 per cent of instances.

4. Simultaneous oral administration of estrogen and progesterone proved slightly superior to progesterone alone but was not sufficient in the dosage used to take the place of estrogen priming in those patients with inadequate intrinsic estrogens.

5. It is believed that best results in management of functional amenorrhea are obtained by cyclic administration of estrogen and progesterone in a manner which closely simulates the normal physiologic process of the ovulatory cycle.

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PHOSPHATE LIBERATION BY ENDOMETRIUM IN THE PRESENCE OF ADENOSINETRIPHOSPHATE*

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STUDIES of an alkaline phosphatase, using glycerophosphate as a substrate, indicate that this enzyme varies during the human menstrual cycle.[1] It was therefore of interest to investigate other phosphate-releasing enzymes in this respect. The present report deals with the biochemical and histochemical variations of phosphate liberation by the endometrium during the normal menstrual cycle in the presence of adenosinetriphosphate (ATP).

Methods and Materials

For the biochemical assays of phosphate-releasing activity the method of DuBois and Potter was used.[2] This measures the rate at which inorganic phosphate is released when a tissue homogenate is added to a solution consisting of 0.45 c.c. of 0.013 M ATP, 0.15 c.c. of 0.041 M $CaCl_2$, and 0.45 c.c. of a veronal buffer.[3] This solution was diluted to 1.95 c.c. with distilled water. These conditions are such that the inorganic phosphate liberated was directly proportional to the tissue concentration and time of incubation. The assays were made at two levels of tissue concentration rather than in duplicate, to provide a better check of the assay. The inorganic phosphate in the tissue homogenates, in the spontaneous breakdown of ATP, and in the reagents, was determined in parallel control tubes and subtracted from the experimental values. Heating to 68° C. for 10 minutes destroys the ability of the endometrium to release phosphate. The activity is expressed as milligrams of phosphorus released from ATP per gram of tissue in 15 minutes at pH 7.4. In order to test the method in our laboratory we assayed rat muscle, kidney, and liver homogenates and found that they released 13.3, 10.6, and 8.4 mg. of phosphorus per gram of tissue, respectively. These values were somewhat lower than those reported by DuBois and Potter[2] but corresponded to those given by Marquette and Schweigert.[4]

The endometrial specimens were obtained by curettage, freed from as much superficial blood as possible by the use of gauze or filter paper, and cooled immediately in a beaker immersed in ice water. Portions of each specimen were fixed in 95 per cent ethyl alcohol for histological examination. If the assay could not be done at once, the tissue was kept chilled between 0 and 5° C. Experiments on duplicate samples of tissue showed that the enzyme activity was not affected by the length of refrigeration time. This finding has also been reported by Marquette and Schweigert for rat liver and muscle.[4]

Since it has been shown that there is no significant variation in the water content of the endometrium during the menstrual cycle,[5] wet weights were considered to be satisfactory. A torsion balance was used to weigh the tissues and a 5 per cent homogenate was made with distilled water. Tissues were homogenized as quickly as possible with the homogenizing tubes surrounded by ice water.

*Aided by a grant from the American Cancer Society, Maryland Division, Inc.

The homogenates were added to the substrate mixtures which had previously been brought to 37° C. in a water bath. One tube contained 0.3 c.c. of 5 per cent homogenate and a second tube, 0.6 c.c. At the end of a 15 minute period, the reaction was stopped by the addition of 0.3 c.c. of 50 per cent trichloroacetic acid to each tube. After centrifugation, an aliquot of the supernatant fluid in each tube was taken for inorganic phosphate determination by the Fiske and Subbarow method.[6]

Histological sections from the alcohol-fixed material were studied to eliminate abnormal cases and dated, using the technique described by Noyes, Hertig, and Rock.[7] Histochemical assays of phosphate liberation were done by an adaptation of Gomori's technique,[8] applied to frozen sections.[9] Slides were incubated from 15 minutes to 20 hours in solutions containing 0.013 M ATP, 0.036 M $CaCl_2$ and veronal buffer at pH 7.4 and 9. Frozen sections and sections of alcohol-fixed material were treated with the periodic acid-Schiff's reagent to attempt a correlation between phosphate liberation activity and glycogen formation.

Results

A total of sixty-eight patients were studied. Thirty-five appeared to have had normal menstrual cycles. In the accompanying bar graph, the results of the normal cases have been summarized. It would appear from these data that a steady increase in activity takes place during the proliferative phase of the cycle. The seven values obtained from the twenty-first to the twenty-third days were consistently higher than those of the previous periods. Although activity was high in some cases after this period, an average of the 24 to 28 day period showed a decrease of about 21 per cent.

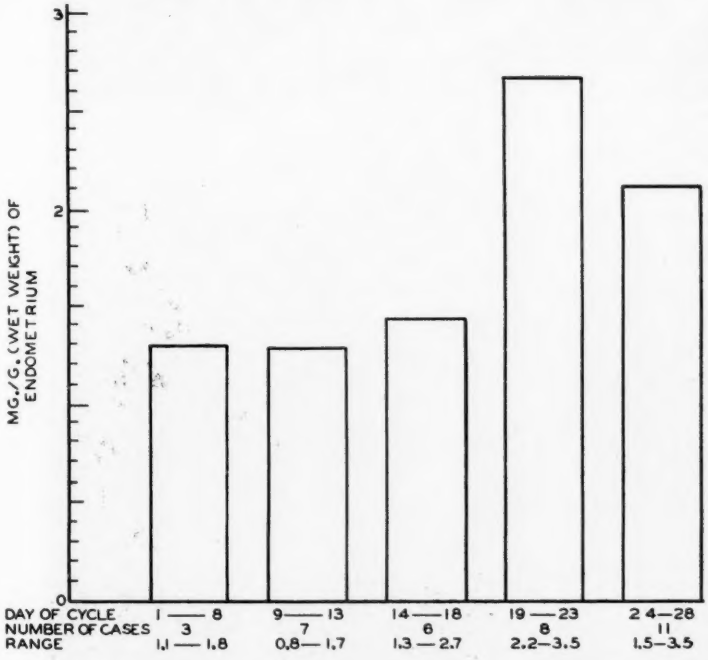

Fig. 1.—Milligrams of phosphorus per gram of endometrium.

The values for phosphate liberation from normal endometrium ranged from 0.8 to 3.54 mg. phosphorus per gram of tissue.

Histochemical studies revealed somewhat different findings in phosphate release at pH 7.4 and 9.

At pH 9 there was high activity throughout the cycle in the blood vessels. In general the stromal cells of the endometrium also showed high activity in all phases of the cycle. However, immediately before menstruation there was some lessening of activity. As can be noted in the photomicrograph, the activity seemed to be confined to the cell membrane. The glandular cells showed high activity in the proliferative phase of the cycle (Figs. 2 and 3) but in the luteal phase phosphate liberation was depressed (Fig. 4). At pH 9 most of the activity seemed to be in the cytoplasm or cell membrane.

Fig. 2.

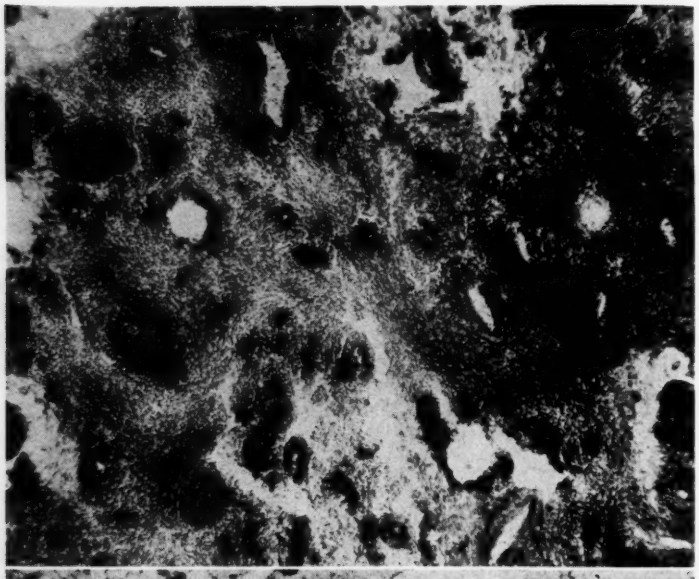

Fig. 3.

Fig. 2 (Case 97738).—Phosphate liberation at pH 9.0; day 5 of normal menstrual cycle. Blood vessels, stromal and gland cells all show heavy concentration of activity. (Three hours' incubation.)

Fig. 3 (Case 97738).—Periodic-acid Schiff's reaction; day 5 of normal menstrual cycle. Little or no glycogen in stroma or glands.

It was the impression that there was a marked depression of glandular phosphate liberation coincident with the marked accumulation of glandular glycogen. In order to study this further, serial frozen sections assayed alternately for glycogen and phosphate liberation were studied. For this purpose, an endometrium which showed considerable glycogen variation from gland to gland was selected. By this procedure, it was possible to confirm the fact that, when glycogen was in high concentration, there was little phosphate liberation and vice versa (Figs. 6 and 7).

Fig. 4.

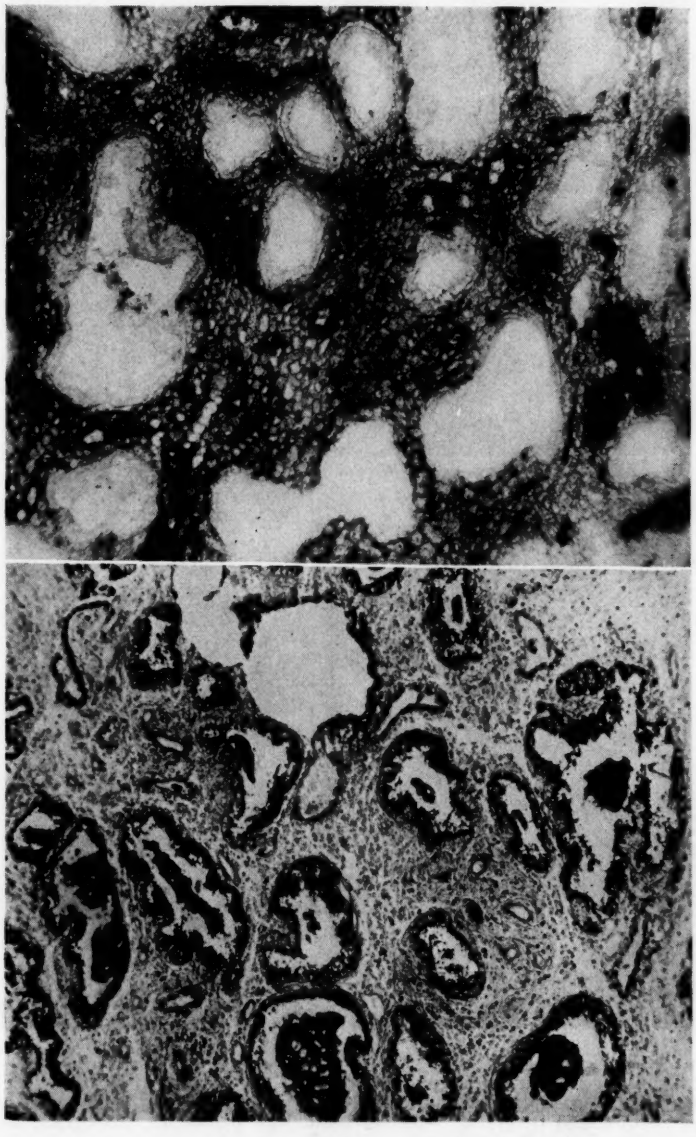

Fig. 5.

Fig. 4 (Case 97261).—Phosphate liberation at pH 9.0; day 20 of normal menstrual cycle. Blood vessels and stroma strongly positive. Glands negative even after 18 hours' incubation.

Fig. 5 (Case 97261).—Periodic-acid Schiff's reaction; day 20 of normal menstrual cycle. High glycogen content of gland-cell cytoplasm.

At pH 7.4, little or no activity was noted in the blood vessel walls. The stromal and glandular cells showed activity throughout the cycle. For the most part, there were strong nuclear and somewhat weaker cytoplasmic reactions. The depression of glandular activity in the luteal phase of the cycle, as noted at pH 9, was not evident at pH 7.4.

Fig. 6.

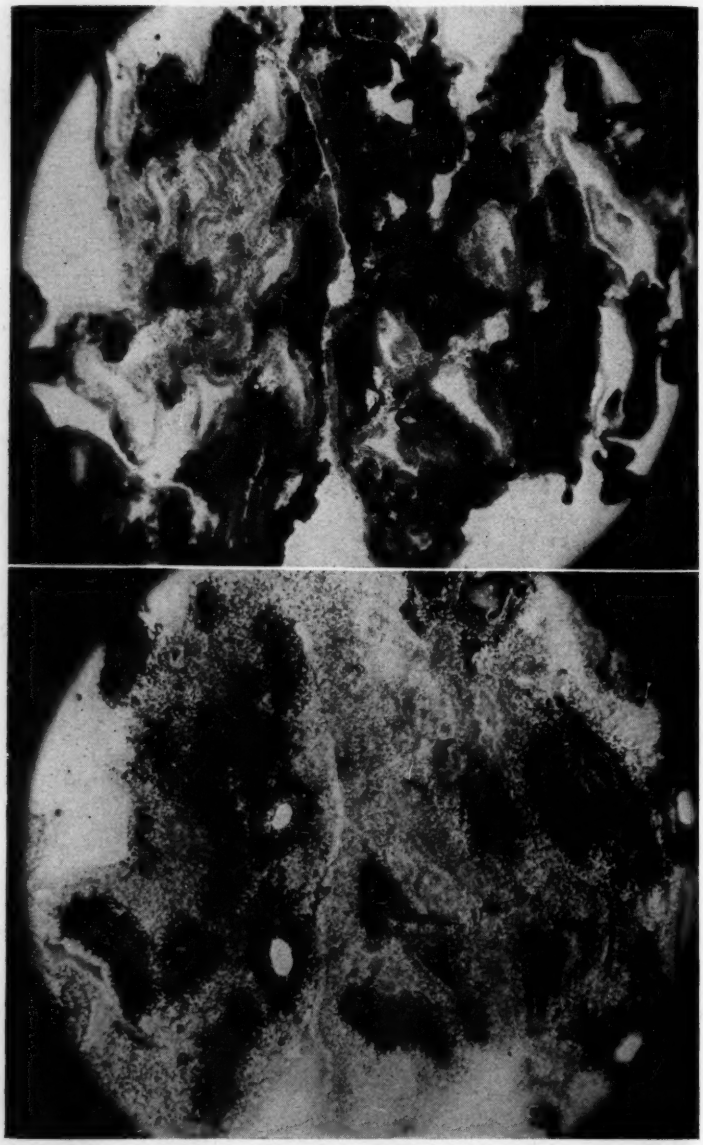

Fig. 7.

Fig. 6.—Phosphate liberation at pH 9.0.

Fig. 7.—Periodic-acid Schiff's reaction. Serial section of endometrium with variation in glycogen content from gland to gland. Glands with high phosphate liberating activity (Fig. 5) have no glycogen (Fig. 7) and vice versa.

Comment

In systems as complex as described herein, it is impossible to designate specifically the enzyme or enzymes involved.

We have no data which would indicate the number of phosphate ions released or their source. The term adenosinetriphosphatase has been rather loosely used in the literature, but should be reserved for an enzyme which releases only the terminal phosphate from adenosinetriphosphate. These studies may or may not be measuring a true adenosinetriphosphatase.

It is unfortunate that at pH 7.4 the histochemical demonstration of phosphate is beset by difficulties arising from the relative solubility of calcium phosphate. The strong nuclear reaction and the general lack of crispness of the sections may be an expression of this difficulty. At pH 9.0 these difficulties are overcome in some measure. The correlation of biochemical work at pH 7.4 and histochemical results at the same pH is open to the difficulties of histochemical localization at pH 7.4. No attempt will be made to correlate biochemical assays at pH 7.4 with the histochemical assays at pH 9.0.

Be this as it may, the highest phosphate-releasing activity, as determined by biochemical means, coincides with the time of greatest pregnanediol excretion and highest blood progesterone levels.[10, 11]

Studies are now under way to investigate in vitro the influence of progesterone and other steroids on the release of orthophosphate from adenosinetriphosphate in homogenate systems.

The histochemical assays at pH 9.0 reveal a remarkable suppression of phosphate-releasing activity in the endometrial glands in the luteal phase of the cycle. The disappearance of glandular activity as the cycle progresses is reminiscent of the situation at pH 9 with glycerophosphate as a substrate.[1] However, there seems to be an intimate correlation between absence of phosphate release in the presence of ATP and glycogen concentration. The fact that glandular and stromal activities differ in the follicular and luteal phases suggests that more than one enzyme is involved. Keilley and Meyenhof[12] have described two types of adenosinetriphosphatase in muscle and this may also occur in the endometrium.

It is interesting to speculate on the possible relation between glandular activity at pH 9.0 and glycogen deposition. The usual concept of the intermediate metabolism of carbohydrates does not include a role for adenosinetriphosphatase or apyrase. However, it is conceivable that, in the endometrium at least, there may be competitive phosphate-releasing enzymes such as apyrase and/or adenosinetriphosphatase with hexokinase for ATP. This concept implies that enzymes which release phosphate from ATP must be suppressed to allow hexokinase to proceed with the phosphorylation of glucose for the entry through the mutase system to glycogen. It may be further supposed that when the adenosinetriphosphatases and/or apyrases are active, the high energy of adenosinetriphosphate is utilized for purposes other than the phosphorylation of glucose. The utilization of this energy for growth immediately suggests itself. If this concept is demonstrated by further studies, the activity of these phosphate-releasing enzymes of the endometrium will have a dominant role in controlling endometrial growth and maturation.

Summary

The release of phosphate by endometrium in the presence of adenosinetriphosphate has been studied by homogenate and histochemical techniques in various phases of the menstrual cycle. Homogenate studies indicate that there is a cyclic variation of phosphate release which is greatest in the mid-progestational phase of the cycle. Histochemical studies at pH 9 demonstrate an intimate and reciprocal relation between phosphate release and glycogen deposition.

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ELECTIVE INDUCTION OF LABOR

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"BABIES by appointment" is a very enticing phrase. What an ideal state if prospective mothers could enter the hospital on an appointed day and be started in labor under ideal conditions. The fears of anesthetic deaths from the aspiration of stomach contents would be avoided, and the dangers and hazards encountered by precipitate labors outside the confines of the hospitals would be almost obviated. Even our overcrowded hospitals might be aided by the staggered admissions of maternity patients and the usual feast or famine of beds be avoided.

We must remember, however, that safety of mother and child is the prime requisite. Therefore, we do not advocate the principle expressed by Miles,[1] that "a woman who has endured a pregnancy to term should be offered the option of being relieved at an appointed time." Nor, on the other hand, do we adhere to the belief of Stewart[2] or Gibson[3] that indications for induction are purely medical and "any unnatural approach to the termination of labor must be justified by urgent reasons." Rather we agree with Greenhill,[4] that "elective induction of labor, when performed at the proper time by one who knows how, carries no risk." As a corollary, we add that the proper patient must be selected for induction. We see no reason for elective induction in the primigravida except in an occasional case, because we have no foreknowledge of the type of labor to be expected or the size of the passenger the pelvis will accommodate. Wallace and Antony[5] and Apthorp[6] share this belief. For elective induction we select patients who have had a previous short labor (8 hours or less), those who live some distance from the hospital, those with progressively larger babies, those with the cervix 3 cm. or more dilated, and those with an anxiety complex or some unusual personal or family circumstances. We regard convenience to the doctor as being purely secondary and not worthy of being taken into consideration.

For elective induction of labor the most important factor in determining the proper patient is the "ripe cervix." This can be determined only by repeated vaginal examinations of the gravid patient as she approaches term. By a ripe cervix we mean one that is at least one-half effaced and admits two fingers. There must be no cephalopelvic disproportion, the baby must be large enough, and the presenting part must be fixed or depressible in the pelvis. There should be no adverse previous obstetrical history. We do not advise elective induction if anything less than these conditions is present.

Many papers have been published recently[1, 5, 7-12] advocating elective induction of labor; few[2, 3] opposed to it. Induction of labor is as old as recorded history but in the early part of this century induction probably reached its peak with Caldwell reporting that 57 per cent of all obstetrical patients at Sloane Hospital had labor induced.[13] The method of induction of labor has varied through the years. Rupture of the membranes was reportedly first used by Soranus in the second century. It was brought into prominence in 1756 when a conference of physicians met in London to devise some method of doing away with the frightful mortality following cesarean section for contracted pelvis.[13] The bougie or rectal tube has also been popular as a method of induction but only recently[14, 15] a comparison of this method with rupture of the membranes has shown its inadequacy. Voorhees is reported to have used a bag for induction in one of four of his private cases.[13] The widespread use of the bag for induction in the early 1900's by unskilled operators led to reaction against induction and cesarean section came into its own.

In the last decade induction of labor by rupture of the membranes has come back to its rightful place but even the method of rupture of the membranes varies. Tennett[16] in England still uses a catheter with a stylet to rupture the membranes and Smythe,[11] believing the forewaters should be preserved, uses a catheter with a stylet in it to puncture the hind waters. Regardless of the method employed, rupture of the membranes is now considered the method of choice for induction of labor. Our technique is as follows:

Procedure

A patient examined vaginally in the office and found to be suitable for elective induction of labor is asked if she wants to be hospitalized and have labor induced. She is not urged to do so but the advantages are pointed out. If she then so desires, the patient is admitted to the hospital having eaten no solid food for at least eight hours. She is prepared for delivery, given an enema, and administered an ampule of vitamin K, following which she is sent to the delivery room. Here the fetal heart sounds, position, and presentation are checked, and 1 minim of pitocin is administered while the obstetrician is scrubbing. This is to keep the head fixed in the pelvis. Under sterile precautions a vaginal examination is made and the pelvis checked. Two fingers are then introduced through the cervix and if no bulging membranes are present the head is slightly displaced and the membranes stripped so as to form a bag of forewaters. A dressing forceps is then used to perforate the membranes while an assistant pushes down on the fundus. A moderate amount of fluid is released while the fingers are kept through the cervix to prevent cord prolapse. After the head is well down in the pelvis a capsule of Nembutal, 1½ grains, is introduced into the rectum and the fetal heart sounds are again checked. The patient is then returned to her bed, the head of which is sharply elevated to keep the presenting part in the pelvis. We rarely use Pitocin after rupture of the membranes, as we have found the need for it very limited in the properly selected induction case. If labor has not ensued in eight hours, we see no contraindication to its use in a 1 minim dose at half-hour intervals. We emphasize the care that must be employed so that there can be no possibility of a mishap. In any elective procedure, every precaution and care must be employed.

Material

We have reviewed 600 consecutive cases of elective induction of labor by rupture of the membranes done at the Elizabeth Steel Magee Hospital. Three hundred were performed by other operators and 300 are our own cases. Elective induction was performed in 6.8 per cent of all hospital deliveries beginning in April, 1949, and going through August, 1950, and in 14.3 per cent of our private cases. No cases are included in which toxemia, diabetes, premature separation of the placenta, etc., dictated the induction. As shown in Table I, 18 per cent of the patients were primigravidas and 82 per cent multigravidas. All patients who had had previous abortions only are classified as primigravidas for the purpose of this study.

TABLE I. GRAVIDITY

Gravida i	108
Gravida ii	246
Gravida iii	149
Gravida iv	51
Gravida v-x	46

TABLE II. AGES IN YEARS

Under 20	14
20-29	351
30-34	160
35 and over	75
Youngest	16
Oldest	45

Ages (Table II) varied from 16 to 45 years with seventy-five patients 35 years of age or over. The duration of the lag-time between rupture of the membranes and the onset of labor is shown in Table III.

TABLE III

LAG PERIOD	TOTAL		PRIMIGRAVIDAS	MULTIGRAVIDAS
1-15 minutes	266		25	241
16-30 minutes	99		14	85
31-60 minutes	73		11	62
1-2 hours	62	97.5%	22	40
2-4 hours	59		23	36
4-6 hours	20		4	16
6-8 hours	6		1	5
8-12 hours	7		5	2
13-16 hours	3		1	2
17-21 hours	1		–	1
22-25 hours	4		2	2

The lag period was eight hours or less in all but 2½ per cent of the cases. We feel a patient ready for induction should have a lag-time no longer than eight hours. Fifteen patients exceeded this limit, eight of whom, or 7.4 per cent, were primigravidas, and seven, or 1.4 per cent, multigravidas. On examining these records, we feel that none of the eight primigravidas fulfilled the necessary conditions for induction. Three subsequently had prolonged labors, one was delivered by version and extraction and three by midforceps. Of the seven multigravidas three had cervices that were not "ripe." There was no explanation of the prolonged lag period in the other four. It may be that too little fluid was released. Only one of the group was in our own series: a gravida iii four days beyond term with a history of previous two- and four-hour labors. Lag period was nine and one-half hours but labor only three hours in duration. The duration of labor is shown in Table IV.

TABLE IV

DURATION OF LABOR	TOTAL		PRIMIGRAVIDAS	MULTIGRAVIDAS
Less than 1 hour	18		0	18
1- 2 hours	132		5	127
3- 4 hours	194	94%	18	176
5- 8 hours	170		40	130
9-12 hours	53		23	30
13-15 hours	16		10	6
16-20 hours	9		6	3
21-25 hours	1		–	1
26-30 hours	2		1	1
31-33 hours	5		5	0

Ninety-four per cent of the patients delivered within twelve hours. This means that the remaining thirty-three patients were in labor from thirteen to thirty-three hours. In a patient, primigravida or multigravida, ready for induction we feel twelve hours of labor a reasonable time. Twenty per cent of the primigravidas failed to deliver in this period. Only 2.2 per cent were multigravidas. In several of these a history of a previous long labor with or without a difficult delivery had apparently been overlooked as a contraindication to induction.

The methods of delivery employed are shown in Table V.

TABLE V

TYPE OF DELIVERY	TOTAL		PRIMIGRAVIDAS	MULTIGRAVIDAS
Spontaneous	99		3	96
Low forceps	444		90	354
Midforceps	22		7	15
Breech extraction	11		3	8
Version and extraction	12	10.6%	4	8
Scanzoni	18		1	17
Cesarean	1		–	1

Excluding low forceps, 10.6 per cent of all deliveries were operative. Primigravidas had 14 per cent operative deliveries and multigravidas 9.7 per cent. The number of breech presentations seems out of line, as such presentations are generally regarded as contraindications to induction. However, four breeches were the second of twins and only one ended with a prolonged labor.

Complicating delivery, there were sixteen second-degree lacrations and two third-degree lacerations. The third-degree lacerations would have been prevented had posterolateral instead of median episiotomies been done. Six uteri were packed and five transfusions given for postpartum hemorrhage. No prolapse of the cord occurred in the series. There was no maternal mortality and the gross fetal mortality for the 607 infants (7 sets of twins) was 2.14 per cent. The causes of death are shown in Table VI. They were all nonpreventable.

TABLE VI

Fetal Deaths		13
Stillborn		5
Macerated	3	
Anencephalus	2	
Neonatal		8
Erythroblastosis	4	
Kernicterus	1	
Sclerema, diaphragmatic hernia	1	
Congenital heart abnormality	1	
Mongolian idiocy	1	

Morbidity, as indicated by a temperature of 100.4° F. or over on two successive days of the puerperium not counting the first twenty-four hours post partum, was 3.16 per cent. Puerperal complications and incidental postpartum surgery are listed in Table VII.

TABLE VII. POSTPARTUM COMPLICATIONS AND SURGERY

Endometritis	13
Pyelitis and cystitis	7
Mastitis	4
Degeneration of fibroid	2
Schizophrenia	1
Retained secundines (dilatation and curettage)	12
Hysterectomy	2
Ligation of tubes	12
Saphenous vein ligation	2
Appendectomy and herniorrhaphy	1
Hemorrhoidectomy	1
Excision of lipoma	1

We wish to repeat that we can see no reason for routine elective induction in primigravidas. In our private cases only 7 per cent (21) were primigravidas and these were carefully selected. None had a latent period of over four hours, but three had labors of over twelve hours. Twenty-nine per cent of the general hospital series were primigravidas. Compared to multigravidas, primigravidas had a lag period of over eight hours five times as frequently; labors over twelve hours, almost ten times as frequently; and operative delivery one and one-half times as frequently.

We would like to cite a few cases in which we feel induction was contraindicated in order to emphasize the necessity of carefully selecting cases for elective induction.

CASE 1.—A 38-year-old gravida iv, para ii, was admitted at term. Her other pregnancies had been fourteen and ten years previously, plus one abortion at six weeks. The labors had been of thirty-eight and forty-two hours' duration, respectively. There was no indication for induction mentioned except that pregnancy was complicated by "severe itching and discharge from the vagina." The cervix was "tough, tense, one-half effaced and 1+ cm. dilated." The lag period was one hour. Labor was four hours in duration and delivery was by low forceps with episiotomy. There was rather profuse bleeding post partum with mild shock. The uterus was packed to no avail. Four hours post partum hysterectomy was performed and, after laparotomy was completed, continued bleeding caused the cervix to be examined and a laceration was found and sutured. Four hours later the patient was again in shock and repeat laparotomy revealed a slipped ligature with a spurting artery. The subsequent postoperative course was uneventful. Contraindications: age, date of last pregnancy, previous long labors, unripe cervix.

CASE 2.—A 37-year-old gravida i, married ten years, a week beyond term with a "funnel" pelvis, was brought in for elective induction. "Cervix was three-fourths effaced, dilated 1½ cm., head high." After a lag period of six hours during which Pitocin was given, the patient started in labor and, after twenty-nine hours of inertial labor, was delivered by low forceps of a 6 pound, 14 ounce baby. Contraindications: age, gravidity, funnel pelvis, station of head.

CASE 3.—A 31-year-old gravida i, at term, had elective induction. "Cervix nearly effaced, dilated 2 cm." The lag period before labor was twelve hours. Labor was thirty-three hours in duration. Then, due to transverse arrest, an internal podalic version and extraction were done with delivery of a 7 pound, 4 ounce baby. Penicillin was given for questionable aspiration pneumonia post delivery. Contraindication: gravidity.

CASE 4.—A 23-year-old gravida iii had labor induced at eight and three-fourths months. She had a history of previous small babies (6 and 6½ pounds). As this was a large baby a

"trial of labor" with membranes ruptured was decided on. The cervix was two-thirds effaced and 2 cm. dilated but after a lag period of thirty minutes and twelve hours of labor an extraperitoneal section was done for "failure to engage." The baby weighed 9 pounds. Contraindications: station of head, size of baby, size of pelvis.

Summary

1. A series of 600 cases of elective induction of labor by rupture of the membranes is presented.

2. The method of selection of patients depending on gravidity, history, and condition of the cervix is described.

3. Eighteen per cent of the patients were primigravidas.

4. The lag period between rupture of the membranes and onset of labor varied from one minute to twenty-five hours. In 97.5 per cent it was eight hours or less.

5. Duration of labor varied from one-half to thirty-three hours. Ninety-four per cent of the labors lasted twelve hours or less.

6. Ten and six-tenths per cent of the deliveries were operative.

7. There was no maternal mortality and the thirteen fetal deaths can all be classified as nonpreventable.

8. Primigravidas had five times as many long lag periods between rupture of the membranes and onset of labor; ten times as many long labors; and one and one-half times as many operative deliveries as multigravidas.

Conclusions

1. Elective induction of labor in the selected multigravida is a safe and justifiable procedure.

2. Elective induction in the primigravida is not advised as a routine procedure.

3. Careful selection of patients is the most important feature in elective induction of labor.

4. Some patients are better served by the obstetrician who judiciously uses this elective procedure. Precipitous deliveries in an undesirable environment and under hazardous conditions are prevented.

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THE EFFECTS OF MORPHINE SULFATE ON CEREBRAL CIRCULATION AND METABOLISM IN NORMAL AND TOXEMIC PREGNANT WOMEN

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THE significant changes in cerebral circulation and metabolism shown in recent studies[1, 2] of women affected by toxemia of pregnancy prompted the institution of a research program to evaluate the effects upon the brain of various drugs and therapies used symptomatically in the treatment of this disease. This was done with the expectation of gaining new insight into the pharmacology of the brain in toxemia and with the hope that a more logical approach to therapy as it affects this organ might be established. The presence of increased cerebral vascular resistance invited the perusal of vasodilator procedures, while the depression in cerebral oxygen metabolism, present in eclampsia and imminent in pre-eclampsia, gave occasion for careful study of the sedatives commonly employed in large doses in this condition. Several drugs have already been evaluated in both of these categories.[3,4,5] This study deals with the effects of morphine sulfate on cerebral circulation and metabolism in normal and toxemic pregnant women.

While opium has been used as a narcotic since the oldest period of recorded history,[6] morphine was not discovered to be its most potent constituent until early in the nineteenth century when Derosne in 1803 and Sertürner in 1805 isolated it from the mother substance.[7] It was not used by injection for a good many years, and it was Fordyce Barker,[8] who, in 1856, was the first in this country to use the hypodermic syringe method of injecting morphine sulfate. For the rest of that century there was great controversy over the injection method of administering morphia until its superiority over rectal instillations in the comatose patient was finally accepted.

Parvin,[9] in his textbook of obstetrics published in 1895, gave credit for the first use of large doses of morphine in eclampsia to Veit of Bonn and Clark of Oswego, N. Y. Stroganoff[10, 11] of Leningrad popularized its use as early as 1897[12] and in 1909 published the lowest mortality statistics for eclampsia ever reported up to that time in a large group of cases, using morphine as a part of his conservative regimen. The influence of this work was widely felt, and in this country many leading obstetricians began using his technique.[13,14] In 1935 the American Committee on Maternal Welfare[15] strongly advised the use of morphine in the therapy of toxemia, and at the present time "modified Stroganoff" methods are used in a great many outstanding obstetric clinics over the world.[16]

The principal pharmacologic responses of morphine are the relief of pain and respiratory depression.[6, 7] While this drug significantly affects other organs and is reputed to exert an antidiuretic action, our study will be confined to its influence on the brain. According to Andrews,[17] usual doses produce no change

TABLE I. EFFECTS OF MORPHINE SULFATE ON BLOOD GASES

PATIENT	AGE (YEARS)	GRAVIDITY	PARITY	DIAGNOSIS	ARTERIAL				INTERNAL JUGULAR			
					O_2 CONTENT VOL. %		CO_2 CONTENT VOL. %		O_2 CONTENT VOL. %		CO_2 CONTENT VOL. %	
					C*	E*	C*	E*	C*	E*	C*	E*
B. L.	35	ii	0	Normal	14.4	14.7	34.6	34.7	8.6	8.4	41.0	40.8
R. W.	17	i	0	Normal	13.5	13.5	44.8	44.9	8.0	8.0	50.2	50.3
L. G.	21	iv	iii	Normal	13.5	13.5	34.8	34.8	6.8	6.7	41.4	41.4
H. H.	16	i	0	Normal	15.3	15.3	42.5	42.6	9.0	9.0	48.9	49.1
L. H.	20	iii	ii	Normal	14.0	14.1	42.6	43.7	8.1	8.2	49.4	49.6
B. J.	25	iii	ii	Normal	13.8	13.9	41.6	41.7	7.5	7.5	48.0	48.1
P. K.	25	ii	i	Normal	15.8	15.7	40.2	40.2	9.5	9.4	46.6	46.5
Mean					14.3	14.4	40.2	40.4	8.2	8.2	46.5	46.5
E. J.	25	iii	ii	Pre-eclampsia	14.6	14.1	38.8	37.4	8.4	8.3	44.9	43.9
†S. W.	33	iv	iii	Pre-eclampsia	13.3	13.7	34.8	35.7	6.8	7.0	41.7	42.6
L. M.	34	vi	iv	Pre-eclampsia Hypertensive	14.8	15.2	36.4	36.8	8.8	9.0	42.7	43.2
N. C.	29	iii	0	Pre-eclampsia	11.5	11.6	46.2	46.2	5.5	5.5	52.1	52.1
M. W.	21	i	0	Pre-eclampsia	12.8	12.9	43.3	43.3	6.8	6.8	49.4	49.4
E. M.	25	iv	iii	Pre-eclampsia Hypertensive	13.0	13.3	41.0	41.2	6.8	7.1	47.2	47.4
C. W.	31	v	iv	Pre-eclampsia	14.5	14.5	44.7	44.5	7.8	8.0	51.1	51.1
D. F.	21	i	0	Pre-eclampsia Hypertensive	14.6	14.6	37.3	37.5	8.3	8.3	44.2	44.2
B. M.	18	i	0	Pre-eclampsia	15.7	15.7	39.5	39.4	9.4	9.4	45.5	45.5
M. H.	17	i	0	Pre-eclampsia	13.5	13.7	34.8	35.0	7.5	7.6	40.9	41.1
†E. W.	28	iv	iv	Pre-eclampsia	15.0	15.1	41.6	41.5	8.5	8.6	48.1	48.0
E. C.	21	ii	i	Pre-eclampsia Hypertensive	15.2	15.2	43.0	43.0	8.7	8.6	49.6	49.6
Mean					14.0	14.1	40.1	40.1	7.8	7.9	46.5	46.5

*C = Control flow.
E = Following morphine sulfate.
† = Completely asleep.

in the electroencephalogram. It does not block motor activity or seriously interfere with consciousness, but its effects in diminishing restlessness and anxiety and in restraining convulsions are well known.

Methods

The method of Kety and Schmidt[18] was used. This involves the simultaneous withdrawal of venous blood from the jugular bulb and arterial blood from the femoral artery over a period of ten minutes while the patient is breathing a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen. Mean arterial blood pressure is measured directly from the femoral artery with a damped mercury manometer. Blood gas analyses of nitrous oxide, oxygen, and carbon dioxide were made with the Van Slyke-Neill apparatus. As previously described,[2] cerebral blood flow (C.B.F.) was measured in cubic centimeters per 100 grams of brain per minute. Cerebral oxygen metabolism ($CMRo_2$) was calculated in cubic centimeters of oxygen utilized per 100 grams of brain per minute, and cerebral vascular resistance (CVR) in millimeters of mercury pressure per cubic centimeter of blood flow per 100 grams of brain per minute. The cerebral respiratory quotient (RQ) was calculated by computing the relationship between the oxygen uptake by the brain and the amount of carbon dioxide given off $\frac{\text{V-A } co_2}{\text{A-V } o_2}$.

Material

Nineteen women were studied. Seven were normal prenatal patients in various stages of pregnancy. Twelve were suffering from pre-eclampsia, in five of whom acute toxemia was superimposed upon mild essential hypertension. All of these women were in the latter weeks of pregnancy or in the immediate postpartum period. No therapy was given for at least twelve hours before the control investigation (C) was carried out. Upon completion of the control flow, morphine sulfate was administered and the patient observed in a quiet room for an average period of one hour. At this time, when the clinical effect of the drug was most manifest, the investigation was repeated (E). One-half grain of morphine sulfate was injected subcutaneously in the fourteen patients who weighed 125 pounds or more and three-eighths of a grain in the five who weighed less. These dosages exerted surprisingly little clinical effect, and only two of the nineteen patients were depressed to the point of sleep while the rest were but moderately drowsy. Respirations were not markedly depressed, and in only one patient did the rate decrease to a level of twelve per minute.

Results

The blood gases as depicted in Table I show that arterial oxygen and carbon dioxide as well as venous oxygen and carbon dioxide do not significantly differ before and after administration of morphine in either the normal or toxemic group of patients.

In normal pregnancy (Table II) there is no significant deviation from normal cerebral function. There was minimal depression of mean arterial blood pressure and cerebral vascular resistance and insignificant rises in the uptake of oxygen by the brain, cerebral blood flow, and cerebral metabolic rate. The respiratory quotient was approximately unity both before and after injection of morphine, showing that carbohydrate metabolism, upon which the brain is so dependent, has not been disturbed.

In the group of twelve nonconvulsive toxemia patients (Table III) there is likewise no change of real significance brought about in cerebral function

by morphine. However, there is a lowering of mean arterial blood pressure from 118 to 109 mm. Hg. There is an increase of only 4 c.c. per 100 grams of brain per minute in cerebral blood flow. The cerebral vascular resistance is decreased from 2.4 to 2.1 mm. Hg per cubic centimeter per 100 grams of grain per minute. The arteriovenous oxygen difference is unchanged at 6.2 vol. per cent, and cerebral metabolic rate in terms of oxygen is increased from 3.1 to 3.3 c.c. per 100 grams of brain per minute while the respiratory quotient remains stationary at 1.01. It is interesting to note that the two patients who were asleep during the second blood flow determination showed no significant variation in blood gases or cerebral function from the patients who were affected less by the injection of morphine.

TABLE II. EFFECTS OF MORPHINE SULFATE ON CEREBRAL FUNCTION OF NORMAL PREGNANT WOMEN

	CEREBRAL											
	MEAN ARTERIAL BLOOD PRESSURE MM. HG		OXYGEN UPTAKE VOL. %		BLOOD FLOW C.C./100 GRAMS BRAIN/MIN.		OXYGEN METABOLISM C.C./100 GRAMS BRAIN/MIN.		VASCULAR RESISTANCE MM. HG/100 GRAMS		RESPIRATORY QUOTIENT	
PATIENT	C*	E*	C*	E*	C*	E*	C*	E*	C*	E*	C*	E*
B. L.	80	80	5.8	6.3	38	40	2.2	2.5	2.1	2.0	1.1	0.90
R. W.	84	80	5.5	5.5	49	49	2.7	2.7	1.7	1.6	0.98	0.98
L. G.	75	81	6.6	6.7	57	60	4.0	4.0	1.3	1.4	1.0	1.00
H. H.	84	70	6.3	6.3	59	64	3.7	4.0	1.4	1.1	1.0	1.03
L. H.	87	87	5.9	5.9	58	67	3.4	4.0	1.5	1.3	0.98	1.00
B. J.	88	74	6.3	6.4	49	50	3.1	3.2	1.8	1.5	1.01	1.00
P. K.	82	80	6.3	6.3	60	67	3.8	4.2	1.4	1.2	1.02	1.00
Mean	83	79	6.1	6.2	53	57	3.3	3.5	1.6	1.4	1.01	0.99

*C = Control flow.
E = Following morphine sulfate.

TABLE III. MEAN EFFECTS OF MORPHINE SULPHATE ON CEREBRAL FUNCTION IN PRE-ECLAMPSIA

	CEREBRAL											
	MEAN ARTERIAL BLOOD PRESSURE MM. HG		OXYGEN UPTAKE VOL. %		BLOOD FLOW C.C./100 GRAMS BRAIN/MIN.		OXYGEN METABOLISM C.C./100 GRAMS BRAIN/MIN.		VASCULAR RESISTANCE MM. HG/100 GRAMS		RESPIRATORY QUOTIENT	
PATIENT	C*	E*	C*	E*	C*	E*	C*	E*	C*	E*	C*	E*
E. J.	117	95	6.2	5.8	59	58	3.7	3.2	2.0	1.6	0.98	1.10
†S. W.	98	91	6.5	6.7	53	65	3.5	4.4	1.9	1.2	1.06	1.03
L. M.	122	113	6.0	6.2	44	53	2.6	3.3	2.8	2.1	1.05	1.03
N. C.	116	102	6.0	6.1	52	51	3.1	3.1	2.2	2.0	0.98	0.97
M. W.	122	117	6.0	6.1	57	55	3.4	3.4	2.1	2.1	1.01	1.00
E. M.	125	122	6.2	6.2	46	49	2.9	3.0	2.7	2.5	1.00	1.00
C. W.	152	142	6.7	6.5	54	51	3.6	3.4	2.8	2.8	0.96	0.98
D. F.	135	122	6.3	6.3	44	47	2.8	3.0	3.1	2.8	1.09	1.08
B. M.	109	102	6.3	6.3	48	60	2.8	3.8	2.3	1.7	0.95	0.95
M. H.	100	106	6.0	6.1	42	41	2.5	2.5	2.3	2.6	1.00	1.00
†E. W.	110	106	6.5	6.5	50	55	3.3	3.6	2.2	1.9	1.00	1.00
E. C.	110	90	6.5	6.6	44	52	2.9	3.4	2.5	1.7	1.02	1.00
Mean	118	109	6.3	6.3	49	53	3.1	3.3	2.4	2.1	1.01	1.01

*C = Control flow.
E = Following morphine sulfate.
† = Completely asleep.

Comment

The results of this investigation show that morphine sulfate, given in adequate dosage to normal and toxemic pregnant women, does not significantly alter the vascular tone, the blood flow, the oxygen metabolism, or the carbohydrate metabolism of the brain.

The mild lowering of blood pressure is probably due to vasodilatation of the skin vessels. Although this peripheral flushing is described in standard pharmacology textbooks,[6, 7] emphasis is not placed upon a hypotensive effect.

Cerebral vascular resistance was decreased 12 per cent. This is thought to be due to a partial release of the vasospasm present in the brain in all toxemias and accounts for a small increase in cerebral blood flow even though systemic blood pressure is less.

Lately studies upon the barbiturates,[4] using the same methods, revealed that Sodium Amytal and Pentothal Sodium, intravenously employed in the minimal amounts necessary to bring about unconsciousness, significantly depress cerebral blood flow and oxygen metabolism while cerebral vascular resistance is increased. In the coma of eclampsia cerebral oxygen metabolism is greatly depressed, and we seriously questioned the advisability of adding the depression of a drug to the depression already existent in the disease.

In the physiologic unconsciousness of normal sleep there is no lowering of cerebral oxygen metabolism.[19] That such a change in cerebral physiology is unnecessary for the loss of consciousness is further shown by the two patients, completely asleep under morphine in our series, whose cerebral circulation and metabolism were as unaffected as in those who were but partially sedated. Morphine, in its action upon the brain, therefore appears to be more physiologic than the intravenously administered barbiturates and certainly exerts less depression on cellular oxygen metabolism.

In conclusion we may state that the quantitative results presented show that morphine neither worsens the measurable functions of the brain in toxemia, nor corrects the pathologic physiology present.

Summary

1. Quantitative studies of cerebral blood flow, cerebral oxygen metabolism, cerebral vascular resistance, mean arterial blood pressure, respiratory quotient of the brain, and the blood gases were made upon 7 normal and 12 toxemic pregnant women before and after the administration of morphine sulfate.

2. There was no statistically significant change brought about upon these functions by morphine, although there was some lowering of blood pressure and cerebral vascular resistance and increase in cerebral blood flow.

3. The effects upon the brain of morphine were compared with those brought about by barbiturates.

4. It was concluded that morphine exerts a more physiologic effect upon the cerebrum than the intravenously administered barbiturates.

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THE EFFECT OF STIGMINENE BROMIDE IN DELAYED MENSTRUATION

A Clinical Study

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THERE are countless numbers of women who believe their menstrual periods occur with unchanging regularity. Yet carefully controlled observations have revealed this as a fallacy, for investigators have shown that variations in successive cycles are considerable. Holt[1] kept exact records of several hundred women for several years and did not find a woman with more than 3 or 4 successive cycles of the same length. A menstrual cycle is occasionally prolonged in an individual who either fears or urgently desires pregnancy or is disturbed by the implications of a functional deficiency. Furthermore, prolonged cycles may portend an undesirable conflict with social or athletic events.

Patients with prolonged cycles frequently request immediate physiologic relief or a positive diagnosis to alleviate the attendant mental stress. When menstruation is delayed for only a few days, the history, physical signs, and biological tests for pregnancy are not often helpful in determining the cause except in those individuals with obvious endocrine dysfunction or pelvic pathology. The usual biologic pregnancy tests are not reliable in very early pregnancy.

In the absence of diagnostic criteria, therefore, the usual procedure in delayed menstruation is procrastination and expectancy. Eventually, menstruation may occur, or the presence of pregnancy be revealed, or the cause of the amenorrhea become highly presumptive or obvious.

Extensive literature has accumulated on the value of cholinergic (parasympathomimetic) drugs to evoke menstrual flow in a prolonged cycle in the absence of disease or early pregnancy. Most reports confirm the value of such agents as a therapeutic measure as well as a diagnostic test for early pregnancy. Reynolds,[2] discussing Soskin's paper, mentioned that injection of a cholinergic drug will precipitate bleeding in the absence of progesterone but will not produce such bleeding in the presence of this hormone. The cholinergic-like action of estrogens is believed to be responsible for the intense and sustained vasodilatation of the uterus in the rabbit during estrus. Pompen[3] showed that atropine, a cholinergic antagonist, will prevent the occurrence of estrogen-induced hyperemia. Herschberg[4] has demonstrated that this hyperemic action is associated with decreased cholinesterase, the enzyme inactivating acetylcholine. Soskin and associates[5] potentiated the naturally occurring acetylcholine in the endometrium by inhibiting the cholinesterase with a cholinergic agent. The effect of cholinergics is based upon the concept that acetylcholine has the important physiologic role of chemical mediation of sympathetic preganglionic

impulses, parasympathetic pre- and postganglionic impulses, and motor nerve impulses.

Since uterine hyperemia appears to be conditioned by the presence of estrogens and by the parasympathetic nervous system, it was reasoned that delay of menstrual flow may result from the influence of stress such as fear, physical exercise, and emotional disturbances upon this division of the autonomic nervous system. This theory has been suggested to justify the pharmacologic rather than the endocrine approach to the therapy of delayed menstruation of non-endocrine origin.

Apparent successful and satisfactory results in the treatment of delayed menstruation by means of cholinergics was the incentive for the present clinical evaluation of Stigminene Bromide.* The use of such drugs is confined to cases in which failure to menstruate occurs in women who are not of menopausal age, who have previously menstruated regularly, and in whom there is no obvious or discernible pelvic disease, systemic disease, or endocrine deficiency.

Pharmacological studies have proved Stigminene Bromide to be a true cholinergic, inhibiting the hydrolyzing action of cholinesterase.[6] Clinical applications have demonstrated that Stigminene has a wide safety margin and is not attended by side effects when used either prophylactically or therapeutically.[7, 8, 9, 10] Furthermore, it proved harmless to gestation and has been found effective in simple delayed menstruation.[11]

Clinical Material and Procedure

A total of 101 private patients, who complained of amenorrhea, were studied over a period of 30 months. Private patients were chosen because of the greater number of women available who are seeking early relief or early diagnosis. Moreover, the necessary follow-ups are more thoroughly controlled. In all instances diagnosis was based upon carefully taken history and complete physical examination. In all cases the Aschheim-Zondek test for pregnancy was made and a biopsy taken where necessary. The duration of amenorrhea before therapy was calculated in days from the expected date of menstruation to the day the first injection was given. The occurrence of bleeding was computed and reported in hours from the last injection administered. If bleeding occurred in any particular case following an injection, this was regarded as an example of delayed menstruation. If, however, no bleeding occurred after the third injection the patient was presumed to be gravid.

Of the total number of 101 patients with a prolonged cycle, 49 received the recommended dosage schedule which consisted of an intramuscular injection of 2 c.c. of a 1:2,000 solution (0.5 mg. per cubic centimeter) or 1 mg. of Stigminene once daily on one to three successive days. The remaining 52 women received an intramuscular injection of 1 c.c. of a 1:500 solution or 2 mg. of Stigminene once daily on one to three successive days. If the amenorrhea was relieved with the first or second injection, further therapy was discontinued. All patients were apprised of the probable effect of the injections and were directed to report the start of the cyclic flow or any symptoms they experienced.

Results

In the group of 49 patients who received 1 mg. doses of Stigminene intramuscularly on each of three successive days, the menstrual flow was elicited

*Stigminene Bromide was supplied through the courtesy of William R. Warner, Division of Warner Hudnut, Inc.

in 34 instances. Their average number of days overdue was 17.3. Twenty-eight (82.4 per cent) of these patients commenced to flow in 6 to 96 hours. The remaining 6 women menstruated in 120 to 192 hours after the last or third injection. In 14 (41.2 per cent) the cyclic flow was re-established after administration of the first or second dose. Clinically, none of these 34 patients showed evidence of pregnancy.

TABLE I. RESULTS OF STIGMINENE THERAPY (1 MG. INTRAMUSCULARLY ON THREE SUCCESSIVE DAYS)

Total number of patients		49
Menstrual flow	34	
Persistent amenorrhea due to pregnancy	13	
Persistent amenorrhea due to causes other than pregnancy	2	

TABLE II. TIME LAPSE BETWEEN ONSET OF MENSTRUAL FLOW AND LAST STIGMINENE INJECTION

TIME	NUMBER OF PATIENTS	TOTAL NUMBER
Within 24 hours	13	13 (38.2%)
Within 48 hours	6	19 (55.9%)
Within 72 hours	5	24 (70.6%)
Within 96 hours	4	28 (82.4%)
Within 120 hours	1	
Within 144 hours	2	
Within 168 hours	2	
Within 192 hours	1	
Total	34	

The Aschheim-Zondek test was made concurrently in 22 of the 34 cases. In one instance the test, reported as positive, proved to be inaccurate. This patient received an intramuscular injection of 1 mg. of Stigminene daily for three successive days and bled within 96 hours after the last injection. A biopsy revealed glandular hyperplasia of the endometrium in the secretory phase without chorionic villi. Her subsequent menstruation occurred after 28 days and was normal in all respects.

Stigminene did not evoke menstruation after a course of three 1 mg. injections in a total of 15 patients. In the light of previous investigations, this would indicate the existence of pregnancy. In 13 instances the pregnancy was subsequently clinically confirmed. Re-examination and a six-month follow-up of the 2 remaining patients disclosed that in one case the delayed menstrual period actually constituted the onset of an oligomenorrhea, the result of endocrine deficiency—an early menopause—in a 37-year-old married woman. In the second case, re-establishment of cyclic flow had not yet taken place in a 19-year-old primipara although parturition had occurred 13 weeks previously. Her cycle prior to the pregnancy had been regular. Normal menstrual cycles were re-established one month following Stigminene therapy. For statistical purposes these 2 patients might be classified as failures in response to Stigminene therapy. However, they actually constitute failures in observing the requirements for the procedure and should have been excluded at the onset. In no instance was a detrimental effect observed upon the gravid state with the use of Stigminene.

The simultaneous Aschheim-Zondek test in this group of 15 patients was interpreted erroneously in 2 cases. Although these 2 women, overdue 65 to 69 days, respectively, had negative A-Z reports initially, they were both proved to be pregnant by subsequent examination and biologic tests. In these 2 instances, Stigminene indicated the presence of pregnancy before the biologic test became

positive. Following one injection of Stigminene, 2 other women did not return for further treatment after gaining knowledge of their positive A-Z tests.

Signs or symptoms of toxic reactions which could be attributed to Stigminene were entirely absent in the group receiving 1 mg. doses of Stigminene. Because of this apparent low toxicity and the wide dosage range as demonstrated by Cohen and Goldman,[10] it was felt that a higher dosage could be given without ill effects. By such dosage, an earlier onset of the menstrual flow in a larger number of patients was anticipated. It was also believed that if there was an appreciable improvement in the results of the two groups the use of a placebo for control purposes would not be necessary.

Accordingly, then, the second group comprising 52 women received 2 mg. doses (1 c.c. of 1:500 solution) of Stigminene intramuscularly on each of one to three successive days. Menstrual flow was elicited in 39 cases. The average number of days overdue was 19.1. In this group, 34 (87.2 per cent) bled in 6 to 72 hours after the last injection; the remaining 5 patients menstruated in 96 to 192 hours. In 19 (48.7 per cent) menstruation took place after the first or second injection. There was no clinical, histologic, or biologic evidence of pregnancy in any of the 39 women. The results achieved with Stigminene were in accord with the simultaneously performed Aschheim-Zondek test in all but one instance. In this case the A-Z reaction was interpreted as positive. However, bleeding began 48 hours following the third injection of Stigminene. Biopsy revealed an endometrium in the proliferative phase with no evidence of pregnancy.

TABLE III. RESULTS OF STIGMINENE THERAPY (2 MG. INTRAMUSCULARLY ON EACH OF THREE SUCCESSIVE DAYS)

Total number of patients		52
Menstruation elicited in	39	
Persistent amenorrhea due to pregnancy	11	
Persistent amenorrhea due to causes other than pregnancy	2	

TABLE IV. TIME LAPSE BETWEEN ONSET OF MENSTRUAL FLOW AND LAST STIGMINENE INJECTION

TIME	NUMBER OF PATIENTS	TOTAL NUMBER
Within 24 hours	21	21 (54.1%)
Within 48 hours	8	29 (74.4%)
Within 72 hours	5	34 (87.2%)
Within 96 hours	1	
Within 120 hours	2	
Within 144 hours	1	
Within 168 hours	0	
Within 192 hours	1	
Total	39	

In 13 cases, Stigminene did not elicit menstrual flow after a course of three 2 mg. injections. This suggested pregnancy which was subsequently clinically confirmed in 11 patients. In 2 cases in which bleeding did not occur there was no clinical evidence of pregnancy and the A-Z tests were negative. Endometrial biopsy disclosed an atrophic endometrium in 1 case; in the other, menstrual flow had not yet been re-established although the patient was 29 weeks post partum. In this latter case, three doses, 4 mg. each, were administered intramuscularly in the customary manner. The results in these 2 cases are similar to those encountered in the group of patients receiving the course of 1 mg. injections; the absence of flow can be charged to an endocrine disturbance. On the basis of the same criteria as applied in the first group, these 2 women should not have

qualified for participation in this study. These cases emphasize the importance of the proper selection of patients for this procedure.

The concurrent Aschheim-Zondek test gave an incorrect result in one case. A negative A-Z test was reported in a woman who was 14 days overdue at the time of the test. Pregnancy was definitely established by subsequent events.

No toxic manifestations or side effects such as abdominal cramps were observed following injection of even the 2 mg. doses of Stigminene.

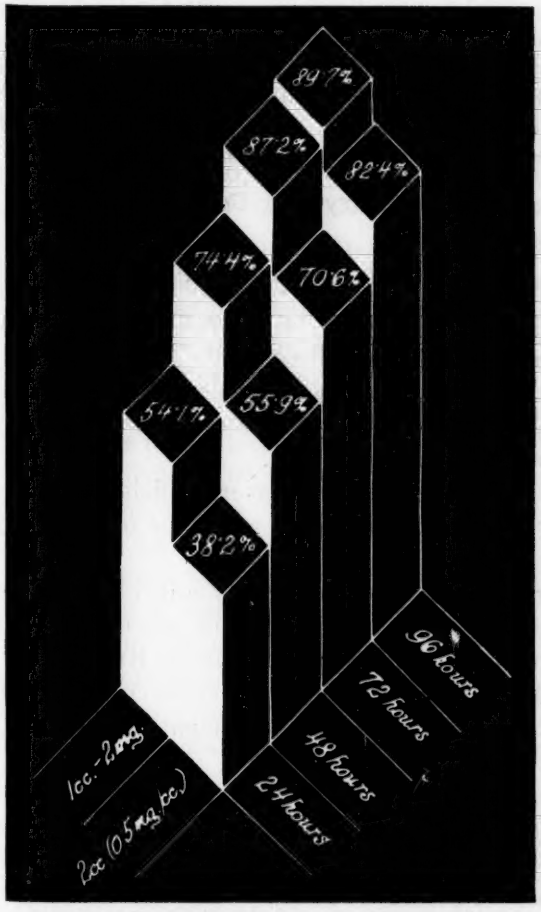

Fig. 1.—Comparative results in delayed menstruation with 1 and 2 mg. doses of Stigminene.

Comment

A comparison of the results obtained utilizing 1 mg. doses of Stigminene intramuscularly once daily on one to three successive days with those achieved employing a 2 mg. dose is graphically presented in Fig. 1. An analysis of the findings obtained in this study reveals that when the 2 mg. doses of Stigminene were administered, the majority, i.e., 87.2 per cent of nonpregnant patients, menstruated within 72 hours, although the average duration of amenorrhea was longer than in the group receiving the 1 mg. doses. Of the nongravid women who received the smaller doses, only 70.6 per cent bled within the same period of time. The remaining patients in both groups finally menstruated within 192 hours. In the group receiving the larger doses, 7.5 per cent more responded to only one or, occasionally, two injections. In other words, when the 2 mg. dose

of Stigminene was employed, onset of menstruation was elicited in a larger number of patients within a shorter period of time and required fewer injections. It would therefore appear that in the treatment of delayed menstruation optimal results may be expected from the administration of a 2 mg. dose of Stigminene once daily on one to three successive days. Furthermore, when bleeding fails to occur, a presumptive diagnosis of early pregnancy may be made after 192 hours have elapsed following the third injection.

In all instances where menstruation was not induced, the presence of pregnancy or an endocrine disturbance was subsequently established. On 2 occasions when menstrual flow was elicited in the presence of a positive A-Z test (Friedman Modification) biopsy did not reveal pregnancy. In 4 instances, the A-Z test was reported negative, menstrual flow was not induced, and the presence of pregnancy was later established. In these instances the Stigminene test was "positive" (no bleeding evoked) at an earlier date than the biologic test.

Summary and Conclusions

1. Stigminene Bromide was used to elicit menstruation in 101 patients in whom there was an average delay of 18.1 days.

2. In the absence of pregnancy or endocrine disorders producing amenorrhea, menstrual flow was evoked in each case.

3. In a group of 49 women with an average delay of 17.3 days, bleeding was elicited in 82.4 per cent within 96 hours after one to three injections of a 1 mg. dose of Stigminene Bromide.

4. In a group of 52 women with an average delay of 19.1 days, bleeding was elicited in 87.2 per cent within 72 hours after one to three injections of a 2 mg. dose of Stigminene Bromide.

5. No signs or symptoms indicating any adverse effects on pregnancy, and no undesirable side effects were encountered in any instance with the administration of either a 1 mg. or 2 mg. dose of Stigminene Bromide.

6. In the absence of pregnancy and endocrine disturbances Stigminene Bromide appears to be effective in the treatment of certain types of functional amenorrhea.

7. In the absence of endocrine disturbances, organic pelvic lesions, or systemic disorders, when bleeding fails to occur after 192 hours have elapsed following completion of a course of Stigminene Bromide injections, a diagnosis of early pregnancy may be made.

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SURGICAL MANAGEMENT OF POSTPARTUM HEMORRHAGE WITH PARTICULAR REFERENCE TO LIGATION OF UTERINE ARTERIES

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AN APOLOGETIC foreword should introduce common and often time-worn subjects, but in this instance I feel that postpartum hemorrhage and its management require no such prefatory excuse. For this complication of pregnancy is at once the most common, most menacing, and most deadly, albeit most preventable, of all the hemorrhagic threats to the parturient. Our experience differs little in this respect from that of the other clinics. It is almost as common as placenta previa, placental abruption, and rupture of the uterus combined. Our definition of postpartum hemorrhage is blood loss in excess of 500 c.c. for the first day after birth. The initial blood loss serves as an avenue for the advent of shock and puerperal infection which so often accompany it. While the incidence of postpartum hemorrhage in our clinic is good by comparison, it is poor by possibility, for I am sure it can be reduced here as elsewhere.

A few words on the causes of postpartum hemorrhage are in order since treatment to a certain extent is conditioned by the causative pathology. First, we have systemic diseases of hemorrhagic nature in which bleeding from the birth tract is merely a manifestation of a general tendency. In recent years we have had two fatal cases of thrombocytopenic purpura which would fit into such a group. Obviously, the obstetric hemorrhages encountered are related but totally subject to the systemic disease.

The second group comprises those which are totally dependent upon the pregnancy. From the obstetrician's standpoint these could be subdivided into those which are nonpreventable, due to circumstances beyond control of the operator, and those which are preventable, in which failure to assess properly a given situation and apply adequate means of therapy permits them to get out of hand. The physician cannot control the development of hydramnios, multiple pregnancy, baby's weight or size, and moldability of the fetal head. Neither can he alter the inherent capacity of the vaginal tract to dilate adequately for the passage of the given fetus. Succenturiate placental lobes may be present and not detectable. Lacerations of the cervix and vagina of serious extent may accompany otherwise perfectly normal vaginal delivery. Last month one of my own patients, without disrupting the perineal skin, produced a perfect Schuchardt incision which hemorrhaged profusely while caput was in sight. But in spite of what has been said thus far, the vast majority of the causes of postpartum hemorrhage are preventable and are the direct responsibility of the obstetrician. These involve most lacerations, retention of secundines and placenta, and atony

of the uterus. So well known is the role played in the production of this condition by deep general anesthesia, long labor, exhaustion, forceps and breech delivery, version and the like, that it scarcely needs more than recollecting.

In reviewing our deaths and near deaths from postpartum hemorrhage, a fact that stands out stark and clear is the role played by uterine atony, which to me is synonymous with mismanagement of the third stage of labor. Unless the physician is aware of the patient's blood status during her pregnancy and at the approach of labor, he is in no position to estimate her capacity to stand blood loss. The onset of shock after a prolonged loss of blood from vaginal or perineal lacerations is as ominous as a sudden gush from a relaxed uterus. A seemingly good physical status in the face of considerable blood loss is of small comfort to the well-advised doctor, since he is aware that he has no means at hand of assessing the patient's capacity to withstand further blood loss nor her proximity to the edge of "compensation plateau" from which she may plunge into a state of shock which might well be irreversible. Unless we remain keenly aware of this possibility, I can see a sharp rise in loss of patients from postpartum hemorrhage because of the progressive scarcity of nursing personnel upon whom we rely for postpartum care.

Mismanagement of the third stage of labor submerges all other causes of postpartum bleeding. While previously mentioned noncontrollable obstetric causes frequently engender hemorrhage, sensible manipulation or, more properly, nonmanipulation of the uterus in these patients will aid the physiologic processes which terminate postpartum bleeding. These uteri bleed because they fail to contract, or the blood fails to clot, or there is a failure in the usual shutdown of the arcuate and spiral arteries, failure of the usual involutional regression of blood flow immediately post partum or because of ill-advised uterine manipulation subsequent to the delivery of the placenta. The oxytocics are generally employed with sense, the patient's blood type is known and suitable blood is readily available, but little training is given the individual delegated to watch the uterus and the still anesthetized patient. Most commonly one sees the uterus massaged, mauled, squeezed, and pushed down into the pelvis and toward the perineum from which it is now normally retracting. The enlarged and firm corpus, containing physiologic clots which are blocking the sinuses, is now squeezed with vim and vigor and all eyes pop as the clots drop from the introitus. After all, what other should one expect? The proper procedure is to draw the uterus out of the pelvis, compress the lower segment against the promontory of the sacrum, gently stimulate the fundus, and encourage the formation of the intrauterine sinus-sealing clot formation. In the meantime, Ergotrate or preferably intravenous Pitocin by drip will tend to maintain the contraction already effected and rarely will there be need for gymnastics such as bimanual compression with one fist in the vagina or uterus. For all practical purposes, we never pack the vagina or uterus in these patients. Almost all of the few we did pack died or continued to hemorrhage. A plug of gauze in the uterus makes an ostrich out of the doctor who does not wish to see what he knows is there. Just as there is an immediate increase in the blood flow to the uterus at the time of conception and even before nidation, so with the delivery of the

fetus and placenta there is an immediate lessening of the blood flow through the uterine artery. If the blood clots in the sinuses are undisturbed, if some contraction and retraction of the uterus can be induced, the lost blood replaced and the patient well oxygenated, there is need for little else. The salutary effect of proper management of the third stage of labor on postpartum hemorrhage incidence has been well shown by Dieckmann, who reduced his incidence from 1.36 to 0.35 per cent through proper control of the third stage of labor.

In considering surgical management of postpartum hemorrhage one should refer first, of course, to the most obvious causes, which are lacerations of the birth tract. There is no justifiable excuse for any patient bleeding herself into shock from lacerations of the cervix, vagina, or perineal body. The only requisites aside from ordinary capability are good light, good anesthesia, good assistance, and, most importantly, good exposure. Every patient who continues to bleed after the delivery of the placenta should have the uterus explored manually. There is no other way to be sure that a succenturiate lobe is not present and it is the only way one can be reasonably sure that there is no laceration of the lower segment or high extension of a cervical laceration. The placenta should be removed manually if it fails to deliver within twenty minutes to a half hour. The old concern regarding manual removal is no longer warranted. Under reasonably good aseptic measures and with the antibiotic drugs which we now possess and which are always given, there should be no mortality attendant upon this procedure. Prompt information is obtained as to whether or not the placenta is retained, adherent, or whether or not one is dealing with placenta accreta. In the last instance an entirely different method of management may be indicated. However, we are no longer in a hurry to remove the uterus for placenta accreta if there is no bleeding. The threat in bygone days was infection but in the absence of gross hemorrhage we now believe this is controllable, and judicious temporizing may save the uterus.

In the overwhelming percentage of cases, the measures already referred to are sufficient. More blood is always given than the estimated loss, since the estimate is always deficient. Oxytocics and, most valuably, intravenous Pitocin solution and adequate oxygenation reinforced by constant and intelligent observation carry these patients safely through the ordeal. Some postpartum hemorrhages of very great severity will respond to such nonoperative treatment. We recently had a patient, bleeding supposedly from recurrent uterine atony, but actually from a retained succenturiate lobe, come close to death before the uterus was emptied of the placental remnant. It was then held in the manner previously described and sufficient supportive treatment was given to bring her through, including 7,500 c.c. of blood. There are a number of cases, however, in which in spite of all that has been done the patient still continues to bleed in volumes equal to or exceeding that which can be replaced. What now can be done for these patients? The usual procedure is to get the patient in as good condition as possible, certainly out of shock and well oxygenated to compensate for some of the blood loss, explore the uterus, and then do a rapid hysterectomy. This has been assumed the only means available to thwart disaster and it is the only one mentioned in almost all standard texts and writings. *I do not believe*

it is necessary, with rare exceptions. Furthermore, the surgeon in so doing is seriously disregarding the rights of the patient and offering little protection for her life when he has achieved his end, if there is a safe alternative.

Many years ago I advocated bilateral uterine artery ligation in these gravely imperiled women. The basis for the suggestion lay in an experience where the condition upon opening of the abdomen became so desperate that death seemed at hand. The large boggy uterus was ballooned with blood and clots, the patient pulseless, and forced respiration maintained with the anesthetic machine. A quick ligation of the uterine arteries was done in the hope that sudden deprivation of blood supply would induce uterine contraction incident to myometrial hypoxia, as well as shut off more than 90 per cent of the blood flow to the uterus. Within a few minutes fibrillary contractions were noted as the uterus responded to stimulation and soon it became blanched and firm. There was no further surgical treatment, but we continued with blood replacement, oxygenation, and oxytocics. Prompt and amazing improvement ensued with ultimate recovery. This experience has been successfully repeated in seven patients under comparable conditions.

Let us briefly consider the varied course and functions of the uterine artery. We know that the uterine artery originates from the anterior hypogastric, that its course is on the lateral wall of the pelvis running medially and forward on the upper surface of the endopelvic fascia and that it is attached by means of its adventitia to and thereby strengthens somewhat the cardinal ligament. We also know it arches over the ureter about 2 cm. from the uterus as the ureter ducks beneath the cardinal ligament in its own fascial tunnel. We know that it gives off a branch to the cervix, the latter anastomosing with the vaginal branches at the lateral fornix of the vagina. In pregnancy, as the progressively enlarging uterus demands more blood, the uterine artery elongates, hypertrophies, and there is a hyperplastic overgrowth of the elastic laminas. It has fibrillary and tenuous connections with the connective tissue at the base of the broad ligament, which make it flexible and vary it somewhat from its normal position in the nonpregnant pelvis. It anastomoses with the ovarian vessels at the upper inner angle of the broad ligament, although its size at this site remains comparable to that in the nonpregnant uterus. This is a matter of some importance, since only uterine artery ligation is projected and not concurrent ovarian artery ligation. The ovarian arteries do not change appreciably in pregnancy. Indeed, there is no reason why they should enlarge. The ovaries do not enlarge nor do they markedly alter in function. Such changes as occur depend upon the early growth of the corpus luteum and this imposes no great demand upon the blood supply. The only alteration of any note is the increase in the venous plexus. Here the ovarian veins apparently assist in carrying away some of the blood from the generally markedly dilated and numerically increased uterine veins.

Likewise, the cervical branch of the uterine artery does not share the same degree of growth. If it did there would be many more fatal hemorrhages from cervical lacerations, since many of the latter are never detected until long post partum. There is no cervical growth comparable to the uterine and since blood supplied to a structure or organ is dependent upon the need or demands, one

logically would not expect an excessive growth of the cervical artery. Over 90 per cent of the blood supply to the myometrium, therefore, is from the uterine artery proper with an inconsequential flow from the ovarian and none of great significance from the cervical. It follows that control of the arterial supply through the main uterine artery should be sufficient to control blood loss from the uterus and with interruption of the well-oxygenated blood flowing to the myometrium there should come a marked anoxic spasm and muscular contraction. This fact is knowingly or unwittingly applied in the medical control of postpartum hemorrhage when the uterus is drawn upward and the lower segment compressed against the promontory. At the same time, the manner in which the uterine artery in pregnancy reaches the uterus makes such medical stricture of its blood flow effective, with diminution of myometrial flow. There is another anatomic fact concerning the uterine artery of practical interest and that is the effect of labor upon its position. In the second stage of labor the cervix descends and immediately post partum it approximates in position a second-degree prolapse. In many primiparas and almost all multiparas the cervix can be prolapsed easily through the introitus with moderate fundal pressure and the artery, now too long for the need, inadequately follows the descensus. The position of the uterine artery is altered somewhat with the descent of the head and the thinning out and effacement of the cervix since it is rather loosely attached to the inner end and upper surface of the Mackenrodt ligament. This obliquity of the uterine artery is an adaptive one and comparable in some respects to the alteration seen concurrent with the growth of lateral cervical fibroids.

These considerations lead to the conclusion that, with normal blood-clotting mechanism, control of the arterial flow to the uterus is the one important anatomic factor required to control bleeding from the structure. Hysterectomy of course does that since it removes the uterus itself. Dependent upon the pathology for which the operation is done, it may be argumentative whether or not the uterus is primarily at fault. Uterine artery ligation will effect the same end as hysterectomy, if the bleeding is from so-called atony.

Many attempts have been made and recommendations offered for vaginal attempt at control of the uterine artery flow. These are generally useless, bloody, time consuming, and needlessly traumatizing. From the anatomic considerations given, especially regarding the altered position of the artery as well as its well-recognized enlargement and increased venous drainage, the vaginal approach is ineffective and is condemned. Based upon false reasoning or more probably none at all, vaginal ligation of the cervical branches has been attempted fruitlessly in many cases in our own clinic for uterine bleeding. It cannot be of any conceivable use, even if successful.

Abdominal uterine ligation, on the other hand, distinctly a surgical procedure, is anatomically sound, physiologically rational, and surgically possible. Of further significance is the fact that it may be used as an initial step to determine whether blood loss will stop and the uterus contract, without compromising the possibility of more extensive surgery. It is a step which must precede all extirpative methods. The artery is ligated, it is not divided. When

the need for ligation arises following cesarean section, the vesicouterine peritoneal plica has already been separated, and the artery is readily found. Exposure in other cases is assisted by similar transverse incision of the vesicouterine peritoneal fold. With the broad ligament grasped so that the thumb is anterior and the fingers lift the base as they slip upward over the uterosacrals, the surgeon can promptly identify the large tough artery. There is no other vessel there except the thin-walled larger veins. After identification, it is surrounded by ligature carrier or blunt needle and strongly tied with No. 2 chromic catgut. The artery is not divided, and later re-establishes its flow. Within five minutes the effect is noted, and has not failed when properly done. Ligating the veins by error of course tends to increase congestion and bleeding. This occurred in two cases in our clinic, where attempted ligation failed and hysterectomy followed. Evidently the veins and not the arteries were ligated, since the uterus was reported to become more dusky and during the subsequent hysterectomy the arteries had to be clamped and ligated. A preliminary successful ligation would have obviated this step.

Summary

In our hands, ligation has not failed when attempted, and we have lost no patients by rejecting hysterectomy. It is distinctly advisable to retain the uterus if it is capable of functioning normally. Where extensive pathology and the patient's age render it useless, it is removed.

There are certain limitations to the procedure of ligation, some obvious and some already noted: (1) When myometrial pathology prevents or inhibits the contractions which the local anoxia induces. This is noted with cervical tumors, fibroids, and excessive myometrial fractionation seen on very rare occasions with placental abruptions. (2) When the veins are mistakenly ligated instead of the arteries. One properly placed ligature is needed on each side, not several blindly placed. (3) When there are intraluminal lacerations involving the cervix. (4) When the uterus still contains placental tissue and membranes, such as were found in many of our hysterectomy specimens. In short, the uterine artery ligation will not surmount basic ignorance and carelessness. It is not offered to eliminate hysterectomy for certain uterine ruptures, atony with huge fibroids, completely obstructive lower segment fibroids, nor as a panacea for bad obstetrics. It *will* overcome obdurate uterine atony without sacrificing the uterus.

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FLICKER FUSION THRESHOLDS IN PREGNANCY

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IN THE course of medical history an early diagnosis has often been accompanied by lowered mortality and morbidity for a given disease. The toxemias of pregnancy are no exception to this observation. For years, weight, blood pressure, and urine measurements have been a part of prenatal care for this reason. Yet the maternal mortality remainder lists toxemia as one of the largest claimants of maternal lives.

With these facts in mind, we welcomed a study of flicker photometry, to confirm or deny it a place in our diagnostic armamentarium. The provocative findings of Brill and associates,[4, 5] as presented a year ago, seemed to make a corroborative study desirable. It is the results of this effort that we wish to report.

Definitions and History

By way of definition[1] flicker fusion threshold (FFT) is that frequency of single periodic stimuli necessary for the retina to fuse single intermittent stimuli into a steady image.

The method of determining this frequency of intermittent stimuli is called flicker photometry.[9]

Though known to the ancients, the phenomenon of flicker was first described by Plateau in 1829.[1] Subsequently it was applied in determinations of retinal physiology by Talbot and Ferry in the last decades of the nineteenth century. Toy manufacturers employed flicker mechanisms to make highly colored tops which produced various images when rotated rapidly. In the last decade FFT was employed by Krasno, Ivy, and others as a means of studying fatigue. This latter use produced a practical machine for determining FFT and it is called the Krasno-Ivy[3] flicker photometer.

This machine consists of a black sphere with a minute clear window which is rotated around a constant steady light source of moderate intensity. The refinements permit variation of the speed of rotation of the sphere, resulting in a variable source of intermittent stimuli. These are cast onto a small ground-glass screen and observed by the patient. A new refinement allows the patient to turn off the machine when the flicker is observed. This allows a constant rate of change of frequency of stimuli by a constant-speed motor and eliminates the human error of the operator manually changing the rate.

Physiology

Because of certain statements we shall later make, we feel a brief review of relevant physiology is in order.

The phenomenon of flicker is dependent upon two factors in retinal physiology,[1, 8, 10] viz.: (1) duration of sensation, and (2) effects of periodic stimuli.

1. *Duration of Sensation.*—Duration of a primary image upon the retina varies, with an average of 0.2 to 0.5 second. Two factors are responsible for this variation.

a. The part of the retina stimulated and its sensitivity. There is greater duration centrally than peripherally.

b. The nature of the stimulating light. In general the duration of sensation varies inversely as the luminosity of the stimulating light.

2. *Effects of Periodic Stimuli.*—If periodic stimuli fall upon the retina in sufficiently rapid succession as to prolong the sensation wave at or near its maximum rise, complete fusion of the separate images results. Therefore, periodic light stimuli, if rapid and uniform in kind, produce the same effect as continuous illumination. However, if the rate is less and stimuli fall upon the sensation curve after the maximum rise, rapid oscillations occur in the resultant sensation, giving a fine tremulous sensation of flicker.

The rate of presentation of successive stimuli which is just necessary to produce complete fusion is called the flicker fusion threshold or the critical fusion frequency of flicker.

A particular numerical flicker fusion threshold value depends on several physical and physiological factors:

1. The nature of the stimulating light
   a. Subjective intensity (Ferry-Porter law)
   b. Its wave length (various colors)
2. Illumination of the surrounding field
3. Retinal area stimulated
   a. Its size
   b. Whether central or peripheral
   c. State of its sensitivity

With regard to size of the retinal area stimulated, an increase raises the fusion threshold. The threshold is higher if several patches are stimulated simultaneously than if they are stimulated separately—a phenomenon demonstrated readily in the peripheral fields but with difficulty at the fovea and illustrating the interaction of retinal fields by summation.

When different retinal areas are compared it is found that for relatively high intensities of illumination flicker disappears first at the fovea (cones) and persists longest at the midperiphery (rods), again falling at the extreme periphery. For low intensities it disappears first in the periphery. It is well known that cones providing photopic vision dominate the central visual fields and rods producing scotopic vision dominate the peripheral fields.

Method

The technique of conducting this test is well laid down by previous investigators.[3] By accident our technique was not in accordance with the standard in that the distance from the screen to the patient's eye was only 4 feet, whereas the standard distance used by Brill and his co-workers[4] was 6 feet.

This variation in our series provided flicker fusion thresholds of scotopic or peripheral fields resulting in higher readings following nitroglycerin administration in normal subjects and lower figures in the nitroglycerin response of abnormals—a complete inversion of the figures obtained by Brill and associates.[3, 4]

By way of explanation in accord with the above-cited physiology and the variables expressed by Landis,[9] we propose that the retinal congestion following nitroglycerin administration provided a dominance of scotopic vision in our patients, thereby resulting in higher fusion thresholds in normal sub-

jects. Improved retinal circulation in abnormal subjects following nitroglycerin administration provided a more dominant photopic vision and thereby a lowered fusion threshold.

The end results are not altered by this variation. In other words, we have been able to distinguish two groups of patients, a normal group and an abnormal group which went on to develop clinical toxemia.

Material

A total of 118 patients from the outpatient obstetrical clinic of Firmin Desloge Hospital were selected for this study. One hundred ten patients completed the study. One hundred five were primigravidas and 5 multigravidas. Fourteen of the primigravidas were Negroes. Of the 110, 6 remain undelivered.

The study was carried out over a ten-month period so that many of the patients were examined in all trimesters of pregnancy.

The medical complications occurring among these patients are noted in Table I and number among them 1 patient with nephritis, 2 with previous toxemias, 1 with epilepsy, 2 patients with heart disease, one congenital and one rheumatic in type, 8 with pyelitis, and 4 with anemia. Thirty-nine of the patients were habitual smokers.

TABLE I

GRAVIDITY		MEDICAL COMPLICATIONS							SMOKERS
		PYELITIS	CHRONIC NEPHRITIS	HEART DISEASE	EPILEPSY	PREVIOUS TOXEMIA	TUBERCULOSIS	ANEMIA	
Primigravidas	105	8	1	2	1	2	1	4	39
Multigravidas	5								
Total patients	110								

Results

A total of 465 tests were performed on these patients during their prenatal visits, an average of 4.2 examinations per patient. This point is stressed as our experience indicates that single tests are inconclusive and that frequent examinations are necessary.

An analysis of the results of the 465 examinations is given in Table II. Here are noted 326 normal tests and 139 abnormal tests. Of the abnormal responses 18 occurred in patients with some of the signs and symptoms associated with toxemia, edema, hypertension, albuminuria, etc. Seventy-nine abnormal tests occurred in patients showing no signs or symptoms of toxemia. Thirty-one abnormal tests were elicited in patients who had smoked within a three-hour period prior to testing. Three abnormal tests occurred in the case of rheumatic heart disease; three in the epileptic patient under treatment; one in a case of thrombophlebitis; one each in 3 cases of pyelitis, and one in a patient who fainted.

TABLE II

Normal tests		326
Abnormal tests		139
With signs	18	
Without signs	79	
Medical complications	11	
Smoking within 3 hours	31	
Total		465

Table III presents a review of 55 consistently abnormal tests in patients who developed and those who did not develop toxemia. As will be noted, 43 consistently abnormal tests were seen in 14 patients who developed toxemia. The majority of these patients in early examinations had shown normal tests and reverted to abnormal responses in the course of pregnancy. Six consistently abnormal tests are noted in the cases of epilepsy and rheumatic heart disease, two abnormal tests in a patient who delivered at 32 weeks without toxemia, and four abnormal responses in a patient delivered at term without complication. Eliminating the cases of epilepsy and rheumatic heart disease as explainable false-positive tests the remaining two cases provide a false-positive percentage of 14 per cent in this series.

TABLE III. CONSISTENT ABNORMAL TESTS

Toxemia		43
No toxemia		12
Epilepsy	3	
Rheumatic heart disease	3	
Prematurity	2	
Term, no complication	4	
Total		55
Percentage of false-positive tests		14%

False-negative results are analyzed in Table IV. Here are noted one patient with nephritis who had three normal tests but developed mild toxemia at term, and one with previous toxemia with convulsions who had normal tests on three occasions, and showed diminished renal function by the usual tests. The third patient with false-negative tests had five normal flicker tests and developed toxemia ten days after the last normal response. This allows a false-negative percentage of 3.3 per cent in the total 326 normal tests.

TABLE IV

Tests indicating toxemia		3
Patients developing toxemia with normal tests		11
Nephritis	3	
Previous eclampsia	3	
Normal 10 days previously	5	
Total consistent normal tests		326
Total false-negative tests		1 or 3.3%

The interval of time from abnormal tests to onset of clinical manifestations of toxemia in the 14 toxemic patients is outlined in Table V. The longest interval was twenty weeks and the shortest one week. The average interval was eight weeks. Fifty per cent were predicted five to fourteen weeks prior to onset of signs and symptoms.

TABLE V. TIME INTERVAL FROM ABNORMAL TEST TO TOXEMIA

NO. CASES OF TOXEMIA	TIME INTERVAL					
	1 WK.	3 WKS.	4 WKS.	5-6 WKS.	11-14 WKS.	15 WKS.
14	1 or 7%	2 or 14%	2 or 14%	3 or 21.5%	4 or 28.5%	2 or 14%
Longest interval: 20 weeks Shortest interval: 1 week						

Finally, each of two patients with toxemia while under management of low-sodium diet alone returned to normal reactions for two and three tests,

respectively, becoming abnormal again before term. One patient on similar management failed to return to normal. All went on to develop toxemia.

Comment

Despite the many factors influencing the determination of flicker fusion thresholds as cited by all investigators writing on the subject[3, 4, 9] any test yielding results in the percentages noted above cannot be denied a place in diagnostic methods. Indeed, clinical diagnosis itself rarely succeeds in a diagnostic accuracy of 86 per cent, not to mention the false-negative minimum of only 3.3 per cent. Many of the laboratory data we are all too prone to accept lack such margins of error.

Haste in acceptance of this procedure is unsolicited, and further corroborative study is urged. Expansion of the method as a measure of effectiveness of therapeutic regimes in these cases is likewise strongly indicated.

No debate is sought with those employing the test in cardiovascular disease,[6, 7] hypertension, and so forth, because we feel that the entity we deal with is pathologically afield from theirs.

The practicability of the test will be greatly facilitated by the introduction of the patient-controlled machine previously mentioned; so much so, in fact, that its use as a routine office procedure is rendered desirable and feasible.

Summary

1. A brief review of pertinent physiology in flicker phenomena is presented.

2. The results of a study of 118 gravid women and 465 flicker fusion tests are presented and analyzed.

3. A false-positive result is noted in 14 per cent and a false-negative in 3.3 per cent.

4. That single tests are inconclusive is stressed.

5. Further study is urged and expansion of application of the method suggested.

Acknowledgments.—Gratitude is expressed to Dr. R. V. Boedeker of the Department of Obstetrics and Gynecology for providing the photometer used in this study and for suggesting the study.

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DIAGNOSTIC VARIANTS IN THE SYNDROME OF ECTOPIC PREGNANCY

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THE standard texts define ectopic pregnancy as a gestation wherein the products of conception are implanted outside the uterine cavity. Difficulty in diagnosis and the serious morbidity of patients exhibiting this accident of pregnancy indicate the repeated need to refresh the diagnostic acumen of the attending physician. It is with this purpose in mind that the 150 cases of ectopic pregnancy were reviewed. The localization of the point of attachment of the placental site to anatomical areas within the pelvic or abdominal cavity determines the variety of ectopic gestation. In the pelvic cavity the placenta may imbed into (1) the ampullar, (2) the isthmic, (3) the interstitial portion or (4) at the ostial end of the Fallopian tube. It may be attached in (5) the tubovarian area, upon (6) the ovary, or (7) the broad ligament. Within the abdominal cavity, the placental attachment may adhere to (8) the mesentery, (9) small or large intestines, (10) the abdominal wall, or (11) other uniquely rare locations upon or over other abdominal organs. The location of the placental attachment bears considerable relationship to the symptomatic syndrome in ectopic pregnancy.

As suggested, the clinical course closely parallels the anatomical location of the placental site of the extrauterine pregnancy. When the ovum implantation occurs in the distal one-third of the Fallopian tube, tubal abortion eventuates usually with a characteristic syndrome. Tubal rupture, with a more severe set of symptoms, is likely to occur at an earlier stage when the ectopic placental imbedding is localized more medially. The ovum which imbeds in the interstitial region of the tube, at its narrowest luminal diameter though in its thicker walled area in the cornual region, may allow the abnormal pregnancy to persist up to three to five months. Once rupture occurs, however, in this area, the symptoms of hemorrhage and shock are profound. Because of the restricted and irregular placental bed, ovarian pregnancies tend to rupture early though a few have been reported as approaching term as secondary abdominal pregnancies. Though relatively few ectopic pregnancies terminate as secondary abdominal pregnancies, they do present serious problems in diagnosis and clinical management.

The usual textbook syndrome of ectopic pregnancy is generally considered by the more conservative authors as being a most uncharacteristic picture. Usually the patients consider themselves pregnant by subjective feel-

ings and about half of them note a "skipped period." They may possibly suffer from slight pain in one or the other lower abdominal quadrant and in rare instances the patient may not even have considered the possibility of being pregnant. There may or may not be an associated interval of menstruation-like bleeding. Often the first manifestation is the sudden occurrence of an intense, lancinating pain in one or the other lower abdominal quadrant. The symptoms of shock usually supervene in severity in direct proportion to tissue damage and blood loss. In slow leakage from small areas of rupture in the first pathogenic phase, or from tubal abortion, the patient may exhibit a slower rate but increasing spread of lower abdominal distress, with or without associated gastrointestinal symptoms. It is because of this mosaic pattern of symptomatic syndrome that may clinics wisely post warnings in staff rooms, in ward offices and over operating schedule boards: Is this case an ectopic?

Material

In the period of this study, January, 1938, to February, 1952, inclusive, there were 17,038 pregnancies cared for at the Metropolitan Hospital. In this interim there were 150 proved cases of ectopic pregnancy treated by surgery, an incidence rate of 1 to each 129 pregnancies, or a percentage rate of 0.776 per cent. Tubal abortions are not included in this series. It must also be recalled that the predominant group in this series is of Puerto Rican descent, though actual statistics are unavailable. This incidence rate is lower than that usually reported in the literature.

Schumann[6] calculated this incidence of ectopic pregnancy to be 1 to every 303 intrauterine pregnancies. He arrived at this ratio by first totaling the number of ectopic pregnancies and adding 10 per cent for those who had died at home from mistaken diagnoses, or who recovered without hospital and/or surgical intervention. He added then 25 per cent to the number of registered births in his series, to account for abortions. This corrected total birth registration figure was then divided into his total number of ectopic cases to obtain his ratio of 1 ectopic to each 303 intrauterine pregnancies. The Metropolitan incidence ratio, 1 in 129 cases, was obtained using a similar formula. Anderson[8] found the incidence of ectopic to intrauterine pregnancy, in the white population at Baltimore, to be 1 in 190 cases and, in the Negro, 1 in 130 cases. Wynne,[10] of Johns Hopkins, reported an incidence of 1.3 per cent of pregnancies. Anspach[11] noted an incidence of 2.2 per cent in Philadelphia.

The age of the patients in this series of 150 cases ranged from 13 to 42 years. Five patients were below the age of 20 years, and 15 patients were between the ages of 36 and 42 years, while the majority, 130 cases, were in the age range of 20 to 35 years (Table I). These findings concur with those reported by Langman and Goldblatt.[7]

TABLE I. AGE INCIDENCE IN 150 ECTOPIC GESTATIONS, METROPOLITAN HOSPITAL, NEW YORK

AGE RANGE	NO. CASES	PERCENTAGE
13-19 years	5	3.3
20-35 years	130	86.7
36-42 years	15	10.0
Total	150	100.0

The gynecological histories of our 150 patients revealed interesting observations. Twenty eight, 18.6 per cent, gave a direct history of previous pelvic

inflammatory disease. Johnson[9] found 22 per cent of his series had a similar history. MacFarlane and Sparling[5] reported 17.2 per cent of their patients gave a history of prior pelvic inflammation.

One hundred thirty-two (132) patients, 88 per cent, gave a history of previous obstetrical difficulties. Primary or secondary sterility histories were found in 56 women, 37 per cent of the 150 cases in the series. It is well recognized that the patient who exhibits difficulty in becoming pregnant has an increased incidence of potential ectopic pregnancy. Eleven of the 150 patients, 7 per cent, gave a history of previous ectopic pregnancy. Henderson and Bean[12] reported a similar figure, while Draa and Baum[4] noted an incidence of 3.5 per cent repeated ectopic pregnancy.

Menstrual irregularity is not a common finding in the history of women having ectopic pregnancy. Some irregularity occurred in only five of our 150 cases, 3.3 per cent. In 14 patients, 9.3 per cent, dysmenorrhea was elicited in their histories.

Approximately three-fourths of the patients in this series told of a "missed period," the remainder noted a prolonged expected period with irregular bleeding or a delayed period with irregular bleeding. *Pain, however, was the most important single symptom.*

Pain was classed as lancinating in one or the other lower abdominal quadrants; crampy and almost constant generalized lower abdominal pain and, less rarely, referred shoulder pain. A sudden "stabbing" or "tearing" pain accompanied with syncope, or syncope with dizziness were classical complaints. Pain in one form or another was present in 145 of the 150 cases, 96.7 per cent. Marchetti,[3] Bell and Ingersoll,[1] and Langman and Goldblatt[7] report a similar high incidence of pain. Cartoux and Tran-Dinh De[15] noted pain in 264 cases, 88 per cent, among the 301 extrauterine pregnancy cases in their recent series.

Cartoux and Tran-Dinh De[15] report that only 35 patients, 11.3 per cent, exhibited difficulty in urination or defecation.

In this series, 45 patients, 30 per cent, reported the onset of the pain as acute and lancinating in character. Another group of 40 women, 26.6 per cent, first noted generalized abdominal pain; while 60 patients, 40 per cent, observed a crampy, almost constant type of lower abdominal pain. Thirty-six patients, 26 per cent, reported shoulder pain as a later symptom of intraperitoneal hemorrhage.

One hundred twenty-eight patients, 85.3 per cent, had associated vaginal bleeding at the time of their hospital admittances. One hundred thirteen women, 75.3 per cent, presented a history of missed periods, while 27 patients, 18.7 per cent, noted a coincidental, else a prolonged and anticipated catamenia. Cartoux and Tran-Dinh De[15] observed vaginal bleeding in 62 per cent of their cases and syncope or vertigo in 42 per cent of their 301 cases. In only 10 cases, 6 per cent, of those studied did bleeding occur *prior to the normally* expected menstrual period (Table II). Cartoux and Tran-Dinh De[15] observed that in 23 of their patients among the 247 presenting a concise menstrual history, there had been no delay in the menstrual periods.

TABLE II. RELATIONSHIP OF VAGINAL BLEEDING TO REGULAR MENSES

	NUMBER OF CASES	PERCENTAGE
"Missed" menses	113	75.3
Prolonged but anticipated regular period	27	18.7
Bleeding prior to regular anticipated cycle	10	6
Total	150	100.0

In 88 women, 58.7 per cent of the series, vaginal bleeding preceded the appearance of abdominal pain while bleeding appeared *with* the onset of pain in 27 women, 19 per cent, and vaginal bleeding appeared *after* the onset of abdominal pain in 30 cases, 20 per cent (Table III).

TABLE III. RELATIONSHIP OF VAGINAL BLEEDING TO ULTIMATE ABDOMINAL PAIN

	NUMBER OF CASES	PERCENTAGE
Vaginal bleeding preceded abdominal pain	88	58.7
Vaginal bleeding and pain occurred simultaneously	27	18
Vaginal bleeding after onset of pain	30	20
Vaginal bleeding with no pain	5	3.3
Total	150	100.0

Abdominal pain without vaginal bleeding at the time of admittance existed in 22 cases, or 14.7 per cent of the series. Vaginal bleeding without abdominal pain occurred in 5 cases, 3.3 per cent.

Fainting was observed as a sign of intra-abdominal hemorrhage or ruptured viscus in 38 cases (25 per cent). Urdan,[14] of Mount Sinai Hospital, New York City, reported an incidence of syncope or vertigo of 29 per cent in his cases. Langman and Goldblatt,[7] at Bellevue, considered syncope almost pathognomonic of ectopic gestation.

Deep shock was noted in 15 patients, 10 per cent, among our 150 cases. Beacham and his associates[2] observed that 13.6 per cent of their patients at Charity Hospital, New Orleans, were in deep shock. Draa and Baum,[4] Chicago, report a 9.0 per cent incidence of shock, while Langman and Goldblatt, Bellevue, observed an incidence of 11.0 per cent.

Gastrointestinal symptomatology was observed in 42 cases, 28 per cent, in this series of 150 patients. Cartoux and Tran-Dinh De[15] report that only 35 patients, 11.3 per cent, exhibited difficulty in urination or defecation. Many other patients in our series reported vague symptoms referable to the gastrointestinal system, categorized as "uneasiness," flatulence, and loose stools. The majority of such histories were too vague to be considered contributory save as fragmental or suggestive evidence in individual cases. Unfortunately, these symptoms were not sufficiently well classified in the histories to permit proper evaluation.

Two women in this series died of irreversible shock. In both instances the patients were admitted in deep shock. Our mortality rate was 1.33 per cent. Anderson's[8] series revealed a similar rate; Henderson and Bean[12] report a mortality rate of 2.3 per cent while Beacham and associates[2] observed a rate of 2.89 per cent in their ten-year study.

While the availability of blood, antibiotics, and other chemotherapeutic agents have aided considerably in reducing the mortality rate, it is fundamentally the increased awareness of the physician of the possibility of ectopic pregnancy and its variable symptoms by which the mortality rates are being reduced.

Comment

Our study of 150 cases of ectopic gestation, all of which were submitted to surgical management, demonstrates clearly once more the often-recorded concept that this acute entity can be "simply else miserably diagnosed." The symptom complex of extrauterine pregnancy exhibits numerous variants which must be constantly considered in all gynecological patients. The patients in our series were predominantly of Puerto Rican ancestry. We find the

incidence of ectopic pregnancy in this group 1 in 129 pregnancies. Along with other authors we find these patients exhibit a stronger history of previous relative infertility and prior pelvic inflammatory disease. It is interesting to note that in approximately 6 of each 10 cases there was vaginal bleeding prior to the appearance of abdominal pain. Attention to such a single symptom often masks the true diagnosis. When considering vaginal bleeding of any cause in women in the reproductive age range we must be alert to the possibility of ectopic pregnancy.

While shock is the usually expected and late picture in ectopic pregnancy, it is well to remember that it actually was present only 10 per cent of the time as reported in this series. Delay in recognition of other variants in the symptomatic syndrome of ectopic pregnancy would obviously increase the percentage of patients admitted in shock condition. Two patients in our series, 1.33 per cent, died in irreversible shock occasioned by prolonged delay prior to hospital admittance for surgical attention. The pathology and operative findings will be presented in a subsequent article.

Conclusion

At the Metropolitan Hospital, there were 150 proved cases of ectopic pregnancy in the 14.2 years between January, 1938, and February, 1952. Two of these patients died.

These 150 patients exhibited complex variants in the syndrome which are considered in detail. In the final analysis, all bleeding and abdominal pain occurring in women under the age of 40 must be considered as possible ectopic pregnancies until *additional and rapid studies* indicate another definitive diagnosis. Particularly in the young woman between 20 and 35 years of age must we remain ever alert and ask ourselves again and again and again—Do these symptoms indicate the presence of an extrauterine pregnancy?

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RECURRENCE OF TUMOR AFTER TOTAL HYSTERECTOMY FOR CARCINOMA IN SITU

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TOTAL hysterectomy is widely regarded as a certain cure for carcinoma in situ of the uterine cervix.[3, 4] Cases reported here suggest that this is not always so.

It has been shown that carcinoma in situ of the cervix is usually a slow-growing lesion. Intervals as long as seventeen years between the first observed intraepithelial lesion and subsequent development of invasive cancer have been noted.[2] Months or years after little or no treatment of this lesion there may be no demonstrable evidence of it, suggesting that invasive cancer does not invariably follow and that, indeed, spontaneous regression of carcinoma may occur.[2, 8]

However, in a few cases recurrence following hysterectomy or full doses of radiation has been observed. Te Linde[7] reported a single recurrence in a series of 108 cases treated adequately and followed. The recurrence occurred following radiation and the patient died of invasive carcinoma within six months of treatment. Schiller[5] reports three recurrences of frank malignancy following hysterectomy for "early" carcinoma. Two of these occurred in a series of 51 cases followed five years. Recently three cases of intraepithelial carcinoma with recurrence after total hysterectomy have focused our attention on this problem.

Fig. 1.

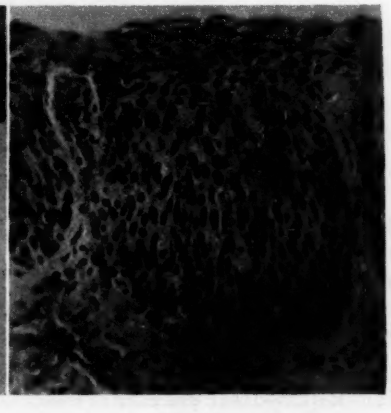

Fig. 2.

CASE 1.—Unit No. 179266. Aged 46 years, para ii. Patient complained of postmenopausal bleeding and was found to have a cervical polyp and endocervicitis.

4-8-39	Total hysterectomy	Histopathology—carcinoma in situ of cervix (Fig. 1)
	CLINICAL EXAMINATION	SMEAR
2- 3-45	Negative	Negative
9-22-45	Negative	Negative
1- 8-49	Negative	Positive, carcinoma
4-20-50	Negative	Positive, carcinoma
5- 4-50	Negative	Positive, carcinoma
6-22-50	Negative	Positive, carcinoma
7-26-50	Partial vaginectomy	Histopathology—carcinoma in situ (Fig. 2)
12- 7-50	Negative	Negative
7- 5-51	Negative	Negative
10- 4-51	Negative	Negative

CASE 2.—Unit No. 497777. Aged 71 years, para ii. At age 51 treated with radium for menorrhagia.

Fig. 3.

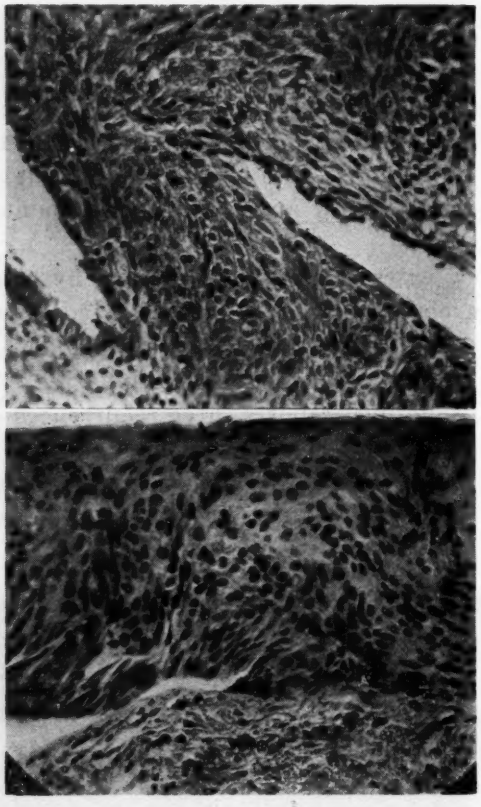

Fig. 4.

2- 2-45	Seen for a routine examination. Clinical examination, lacerated cervix	Vaginal cytology, positive, carcinoma
7-24-45	Hysterectomy	Histopathology—carcinoma in situ of cervix (Fig. 3)
10- 9-45	Clinically negative	Vaginal cytology, negative
11-14-51	Returned for premarital examination. Clinical examination, slightly suspicious	Vaginal cytology, positive, carcinoma
	Patient refuses further treatment	Histopathology—carcinoma in situ (Fig. 4)

CASE 3.—Unit No. 318938. Aged 40 years, para ii. Complained of abdominal pain and was found to have pelvic inflammatory disease.

9-16-41	Total hysterectomy, bilateral salpingo-oophorectomy Histopathology—chronic cervicitis Recent review of sections shows carcinoma in situ of the cervix extending to the edge of the section (Fig. 5)	
7-13-42	Clinical examination—negative	
3-17-49*	3 cm. nodule in vaginal apex treated with 600 mg. hr. of radium in plaque	Biopsy, squamous-cell carcinoma
4-19-49 to 6- 4-49*	X-ray, 200 kv., four 15 by 15 cm. fields, total 8,000 r skin dose	
7-19-49*	1,250 mg. hr. of radium in plaque	
3-17-50*	600 mg. hr. of radium in plaque	
12-19-50	Total exenteration†	Histologic examination showed an epidermoid carcinoma, Grade II
8-20-51	Clinical examination—negative	

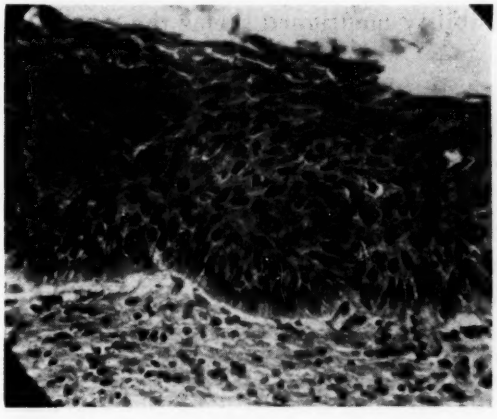

Fig. 5.

Critical aspects of this problem are whether the entire lesion was truly noninvasive at the original observation and whether the entire lesion was removed at the time of hysterectomy. Unfortunately, neither is susceptible of proof. Galvin and Te Linde[1] found that microscopically invasive carcinoma was present elsewhere in 68 per cent of 108 cases showing carcinoma in situ. It must be kept in mind that these authors regard glandular involvement as invasive carcinoma, a view that is by no means universal.[8] However, there can be no doubt that carcinoma in situ does frequently accompany invasive cancer. In fact, the classical description of intraepithelial carcinoma of Schottlander and Kermauner[6] was in cases where it was adjacent to frank malignancy.

In the first case the lesion did not extend to the margin of the specimen and two smears (in 1945) were negative four years before positive smears were obtained in 1949. This course of events suggests that the entire lesion was removed initially and that some time between the sixth and tenth year following hysterectomy the patient developed a new carcinoma in situ.

The second case was discovered by vaginal cytology. The positive vaginal smear was the only evidence of any malignancy, she had no symptoms and the cervix appeared negative except for a laceration. At hysterectomy there was a 1 cm. lesion in the endocervix. Grossly it appeared to be entirely removed

*At another clinic.
†By Dr. Alexander Brunschwig, New York, N. Y.

with a good margin. Additional evidence to support this thesis is a negative vaginal smear three months postoperatively.

In the third case the lesion extended to the edge of the histologic section. The vaginal cuff is not mentioned in the gross description; however, in this hospital the usual technique of total hysterectomy removes about 0.5 cm. of vaginal cuff. Several possibilities exist in this case:

A. An invasive lesion may have been present at the time of hysterectomy but was missed in the sections. Seven and one-half years is a rather long symptom-free interval if invasive cancer was present all the time.

B. Carcinoma in situ extended out on the vaginal wall beyond the area of resection, and subsequently became invasive.

C. The entire lesion was removed at hysterectomy. The more recent invasive cancer was a new development with no direct relationship to the original in situ carcinoma.

The second possibility mentioned seems the most likely from the evidence at hand.

Although the life history of these lesions is obscure, we now have the means at hand to deal with them more successfully than in the past. Armed with the knowledge that carcinoma in situ may recur with fatal implications, a vigilant follow-up system must apply to these patients just as it does to patients treated for more advanced cancer. They must be seen at regular intervals and their examination should include a vaginal smear and Schiller's iodine test at each visit. Biopsy of suspicious or nonstaining areas is essential.

Summary

Hysterectomy for carcinoma in situ of the uterine cervix is not always curative. The lesion may recur as a carcinoma in situ or as frankly invasive cancer. Three illustrative cases are presented, with recurrence six, seven, and ten years after operation. Patients with carcinoma in situ treated by hysterectomy deserve a careful follow-up.

The authors are indebted to Dr. Robert H. Fennell for review and analysis of the histologic material.

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A MANAGEMENT OF POSTPARTUM HEMORRHAGE BY PROLONGED ADMINISTRATION OF OXYTOCICS

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POSTPARTUM hemorrhage remains among the chief causes of maternal mortality, although its fatal effects have been greatly reduced since the advent of blood transfusion. Even though comparatively few of these hemorrhages cause death, they always jeopardize the life and future well-being of the patient, to say nothing of the acute anxiety they inflict on the physician and the family.

Aside from lesions of the birth canal and the retention of placental tissue, atony of the uterus is the main cause of postpartum hemorrhage. This may be either spontaneous or brought about by such predisposing factors as polyhydramnios, multiple births, or many previous labors. Uterine atony may also be secondary to general anesthesia or follow prolonged and difficult labor.

The hemorrhage due to uterine atony usually appears as a steady flow of blood from the vagina a short time after the delivery of the placenta. When the placenta has been expelled the uterus contracts, temporarily closing the uterine sinuses. After a short time, however, it relaxes and becomes "boggy," filling with blood. This is the most deceiving and dangerous type of hemorrhage, as it does not alert the obstetrician at the outset so he fails to observe immediately that his patient is losing blood slowly but steadily, often collapsing suddenly before the danger is realized.

If the uterus remains firm and does not bleed for one or two hours post partum, it is likely to remain so. Acting upon this observation we are proposing a method of treatment for postpartum hemorrhage due to uterine inertia.

To review briefly the anatomy and physiology involved in this condition: The wall of the uterus is composed of three layers of tightly interwoven muscle fibers. The outer and inner layers are relatively thin, composed of fibers which run longitudinally through the wall. The median layer is much thicker, being made up of circular fibers which run in a more or less oblique course, and is very vascular. The three layers of muscular tissue are laced together by many intervening muscle strands and as a result of the crossing and recrossing of these fibers and muscle bundles a complex network is formed enmeshed within which the many blood vessels course.

The normal mechanism which controls uterine bleeding is the contraction and retraction of these many interlacing muscle bundles and fibers. Contraction

of this complex network constricts the blood vessels and uterine sinuses almost as if they had been ligated. Normally this will completely inhibit any bleeding following the delivery of the placenta. Yet this will not permanently stop the bleeding, because no muscle can remain constantly in a state of contraction. It is the ability of the uterine muscle to retract and thus permanently shorten itself which normally keeps the uterus firm and the blood vessels hemostatic. If the uterine musculature is atonic and uterine retraction slow, hemorrhage will recur as soon as the uterus relaxes. Our plan consists in *stimulating the uterus to remain contracted* until the proper time for relaxation arrives.

The usual method of stimulating uterine contraction is with oxytocics and uterine massage. In most instances of excessive bleeding due to uterine atony such prophylactic and therapeutic measures will prove adequate. If not, blood transfusion and other supportive means must be resorted to, plus uterine packing or even hysterectomy. Despite all these measures, however, serious postpartum hemorrhages still take place and fatal outcomes are all too frequent. The lowering of such maternal mortality remains the grave concern of all obstetricians.

At the Cook County Hospital we have seen but few obstetric cases where it has been necessary to pack the uterus. When it has been done, it was usually for didatic rather than therapeutic purposes. It should be remembered that a packed uterus is much more liable to sepsis, and any intrauterine manipulation such as packing invokes the hazard of injury to the uterus. Another consideration is that such packing—unless properly done by a sufficiently skilled operator—serves merely to hide the hemorrhage and give a false sense of security.

From the time of Semmelweis and Oliver Wendell Holmes to our own day, sepsis has been the major cause of postpartum death. Today, however, hemorrhage ranks above it. The Children's Bureau[1] reports that 20 per cent of the maternity cases in the last quarter of record mention postpartum hemorrhage, while 40 per cent of all maternal deaths are due to hemorrhage. In the year 1944-45, 30 per cent of *all* postpartum deaths were from the same cause. Beecham,[2] in 1947, stated that the patients in 41.5 per cent of the fatal postpartum cases had been treated with oxytocics and uterine massage; all of them had received fluids intravenously, and 25 per cent of them had had blood transfusions. But to none had oxytocics been given over a prolonged period. In Illinois[3] the maternal death rate declined from 2.07 per thousand live births in 1943 to .98 per thousand live births in 1947. Hemorrhage still ranked third as a cause of maternal death, accounting for 17.5 per cent of all postpartum fatalities.

It has been shown by Erving and Power[4] that in the majority of cases where hemorrhage proved fatal, the time interval between delivery and death of the mother was approximately five and one half hours. In other words, the situation is not usually one of sudden profuse bleeding with rapid fatality, but rather a slow but steady oozing over a time period long enough to permit suitable action to have been taken.

For the physician confronted with postpartum bleeding, the first procedure is obviously a thorough search of the birth canal for injury or retained placental tissue. If the bleeding proves to be coming from the uterus—retained placental tissue having been ruled out—the customary procedure is to apply uterine massage and to give one or two doses of an oxytocic. This done, the obstetrician is likely to leave the hospital, satisfied that all is well. It is—to say the least—disheartening when he arrives at his destination to be greeted by a frantic summons to fly back to the hospital because his patient is bleeding, despite the oxytocics. Furthermore, even during his hasty return to her bedside a critical period may have elapsed. It is for the saving of such a situation that we propose our method of managing postpartum hemorrhage.

The regularly employed oxytocics, posterior pituitary extract (Pitocin) and Ergotrate, do not have the same effect upon the uterus. Posterior pituitary extract (Pitocin) causes it to contract and relax rhythmically, the duration of its action being from twenty to thirty minutes. The contraction induced by Ergotrate is, by contrast, of a tetanic type, the effect of the drug persisting for an hour, or even an hour and a half. Keeping these facts in mind, the rationale behind the methods proposed is easily comprehended.

Proposed Method

During a study on the management of labor prolonged by uterine inertia, we noted that when posterior pituitary extract (Pitocin) was subcutaneously administered its maximum effect was maintained for from twenty to thirty minutes. We reasoned that inertia of the emptied uterus might be offset by the frequent administration of small doses of this agent. This plan was later expanded by using alternating doses of posterior pituitary extract (Pitocin), 5 minims subcutaneously, and Ergotrate, 0.5 c.c. intramuscularly or intravenously, every thirty minutes for four to six hours. This provided constant stimulation for contraction and retraction of the uterine musculature over a prolonged period of time. Later, with the more extended use of dilute posterior pituitary extract (Pitocin) intravenously, we found that a mixture of 1 c.c. to 2 c.c. of posterior pituitary extract (Pitocin) in 1,000 c.c. 5 per cent glucose in distilled water has been proved to give excellent control of excessive bleeding due to postpartum uterine atony.

When hemorrhage can be anticipated—as in abruptio placentae, prolonged labor, multiple births, polyhydramnios, or a history of previous postpartum hemorrhage—prophylactic employment of such agents is advisable. In the actual event of hemorrhage, administration, particularly of dilute posterior pituitary extract (Pitocin), is easy and elicits a prompt response. As a result of the investigations we have made along this line, postpartum packing, a procedure of questionable value, has been practically eliminated from our obstetric practice.

Summary of Case Reports

CASE 1.—D. S., a 19-year-old woman, gravida ii, para ii, was in labor four hours first stage, 20 minutes second stage, 55 minutes third stage. The placenta was manually removed because of bleeding (total loss of 1,000 to 1,200 c.c. blood); the blood pressure following delivery of placenta was 90/50. The patient was given 250 c.c. plasma, 1,500 c.c. whole blood, one ampule Ergotrate intravenously and finally Pitocin in 1,000 c.c. 5 per cent glucose intravenously. One hour later the blood pressure was 100/60, uterus firm with little

further bleeding. The uterus remained firm after therapy, blood pressure was 105/70, and the postpartum course uneventful.

CASE 2.—A. W., a 34-year-old woman, gravida vii, para vii, was delivered of twins after protracted labor (72 hours and 35 minutes) following which the uterus contracted poorly, with loss of 400 c.c. of blood. After a transfusion of 1,000 c.c. of blood the patient was placed on alternate doses of Pitocin and Ergotrate over a three-hour period. Thereafter, she lost no more than an additional 150 c.c. of blood, and the subsequent postpartum course was without incident.

CASE 3.—T. C., a 26-year-old woman, gravida v, para v, was in labor 5 hours first stage, 19 minutes second stage, 5 minutes third stage. Manual extraction of the placenta was performed because of severe hemorrhage. As no blood of the patient's type was available, she was given fluid intravenously and, as a precaution, placed on our Pitocin-Ergotrate routine. Following placental delivery the uterus remained firm. As soon as it was available, 500 c.c. of suitable blood were administered to aid the postpartum course, which proved quite uneventful.

CASE 4.—E. B., a 19-year-old woman, gravida i, para i, had a labor which lasted approximately one hour and thirty minutes in the first stage and 30 minutes in the second stage, with no third stage—placenta and baby being delivered simultaneously. The patient was in active labor on entrance, with the cervix almost completely dilated. Bleeding on admission, she lost some 300 c.c. of blood prior to delivery. The diagnosis was abruptio placentae. Fluids were started intravenously and shortly thereafter a stillborn baby and the placenta were delivered together. The Pitocin and Ergotrate method was employed therapeutically and the uterus remained firm following delivery.

Summary

Two methods of controlling postpartum hemorrhage are described and recommended.

1. Administration of posterior pituitary extract (Pitocin) and Ergotrate in alternate doses, at half-hour intervals, over a period of three to four hours.

2. The use of dilute Pitocin intravenously—1 to 2 c.c. Pitocin in 1,000 c.c. 5 per cent glucose solution.

This prolonged administration of oxytocics to patients with intractable postpartum hemorrhage has yielded us a high degree of success.

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POSTPARTUM INTESTINAL OBSTRUCTION

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INTESTINAL obstruction is a serious condition and may be accompanied by high morbidity and mortality. When complicated by pregnancy, or when occurring in the immediate postpartum period, additional problems in diagnosis and treatment are posed. Intestinal obstruction during pregnancy is an extremely rare condition being reported from one in 7,000 to one in approximately 66,000 pregnancies.[1] During the postpartum interval the condition is even more infrequently found. Only one case during the postpartum period was found in the literature from July, 1942, to July, 1952.[2] Because of the rarity of this complication and its grave prognosis it is believed that the reporting of the following case is warranted.

L. H., HKH No. 120605, a 26-year-old, Negro woman, gravida ii, para 0, was admitted to the hospital March 20, 1952. Her prenatal course had been normal and uncomplicated. On admittance to the hospital she was in active second stage labor with the vertex presenting and 3 cm. below the ischial spines. Under pudendal block anesthesia, over a left mediolateral episiotomy, with the aid of low forceps, a 2,994 gram female infant was delivered without difficulty, twenty minutes after admission.

With the exception of an elevation of blood pressure to 170/110, physical examination following delivery was normal. Pulse rate and temperature were normal. Admission urinalysis was negative.

Past history included an appendectomy in 1950 and salpingectomy for ruptured tubal pregnancy in 1949. She had been successfully treated for syphilis and gonorrhea in 1942. No other medical or surgical diseases were noted.

The patient was admitted to the postpartum ward with the diagnosis of pre-eclampsia, mild, and was started on routine toxemia regime. She remained asymptomatic for 12 hours following delivery at which time she began complaining of cramping abdominal pain and inability to void. Physical examination was negative except for a distended bladder. Upon catheterization, 1,200 c.c. of urine were obtained and the patient became asymptomatic. Twelve hours later, or 24 hours after delivery, she began to complain of constant periumbilical, sharp, nonradiating abdominal pain. Upon questioning, the patient admitted no passage of flatus or feces for 24 hours prior to delivery. Abdominal examination revealed minimal distention with tympany, generalized tenderness, but no rebound phenomenon. Temperature, pulse, and bowel sounds were normal. The uterus was well contracted and palpable below the umbilicus and was not tender. The patient was apprehensive and maintained an anxious expression but reassurance and moderate sedation relieved her symptoms. Six hours later a change in physical findings was noted. Auscultated bowel sounds were now absent and rebound tenderness was present. The temperature remained normal but the pulse rate had increased to 100 and there was an increase in abdominal distention. A diagnosis of ileus, secondary to peritonitis, was made although mechanical obstruction was considered.

A long intestinal tube was passed into the stomach and abdominal x-rays obtained. These films revealed dilated loops of small bowel in the right lower quadrant with gas scattered throughout the small intestine. Sedation, antibiotics and fluids were given. Vomiting was absent, but was probably prevented by gastric aspiration. During the next 24 hours there was no change in clinical findings. However, repeated flat and upright x-ray films of the abdomen were diagnostic of mechanical obstruction. These films showed progression of the small bowel distention, and definite fluid levels in the intestinal loops. Repeated attempts to pass the intestinal tube beyond the stomach were unsuccessful. On the patient's fifth postpartum day, March 25, the classical clinical findings of mechanical obstruction of the small bowel were evident. The abdomen was markedly distended and showed the typical washboard appearance. Visible peristalsis was present. High-pitched peristaltic sounds, with "tinkles" and "rushes," were heard on auscultation. The patient became dehydrated and lethargic, and temperature ranged between 101 and 102° F., and the pulse between 100 and 130. Repeated attempts, under fluoroscopy, on March 25, finally succeeded in passing the intestinal tube beyond the stomach into the duodenum. Within a few hours moderate decompression was obtained, fluids were restored, electrolyte balance achieved and a laparotomy was done.

Upon opening the abdomen constricting fibrous bands were found in the area of the previous appendectomy. A single large adhesive band extended from the base of the mesentery of the ileum to the abdominal appendectomy scar. A loop of ileum was twisted about this adhesion. In this area there was marked edema of the bowel wall and the blood supply was partially compromised. The obstruction was relieved and the large adhesion severed. The obstructed loop regained a satisfactory color and resection was not necessary. Postoperatively the patient recovered rapidly and was discharged home on the ninth postoperative and fourteenth postpartum day.

Comment.—The incidence of intestinal obstruction in pregnancy is small. Block and Sales[3] were able to collect 22 cases from 33 hospitals over a ten-year period. Williams[5] noted two cases in 30,000 pregnancies, and Weintraube and Jaffe[6] reported three cases in 32,000 patients.

In about 60 per cent of the reported cases in pregnancy the obstruction is caused by adhesions and bands. Only 5 per cent are caused by inguinal and femoral hernias. This may best be explained by displacement of the small bowel out of the pelvis by the enlarging uterus. Tumors, cysts, foreign bodies, and pregnancies themselves are other reported factors.

All of the cardinal signs and symptoms of intestinal obstruction may occur in a normal pregnancy, but since torsion of the adnexa or injury to the pregnant uterus are more common, one tends to think chiefly in terms of the genital tract. It is important to note that flatus and feces may be passed in a patient who has small bowel obstruction, and this is paricularly true if the site of the obstruction is high. It is also of interest that, as in this case, symptoms and signs may be minimal when noted early. The diagnosis should be considered whenever the symptoms of colic, vomiting, obstipation, and abdominal distention occur, and particularly when a postoperative abdominal scar is present. Flat and upright abdominal x-ray films may often be diagnostic but at other times show no evidence of bowel obstruction or may be equivocal.

The long intestinal tube introduced in 1937 has been largely responsible for lowering the mortality rate from intestinal obstruction. Smith and Van Beuren[4] report a mortality decrease from 66 per cent (1916-1919) to 24 per cent (1935-1939) in cases of acute ileus. It should be emphasized that use of the long tube in order to delay surgery is dangerous. To wait until there are evidences of strangulation and for increasing distention and electrolyte imbalance before operative intervention is to invite high mortality. Other contributing factors to the decreased mortality rate are: better knowledge of fluid and electrolyte requirements, antibiotics, and the use of blood transfusion.

Summary

A case of a 26-year-old multiparous woman who had had two previous laparotomies, and who gradually developed small bowel obstruction during the first five postpartum days is

presented. Laparotomy was necessary, and the ileum was found twisted around an adhesive band. The adhesion was divided and the patient recovered.

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RUPTURED CORPUS LUTEUM CYST: A POSTOPERATIVE COMPLICATION OF VAGINAL HYSTERECTOMY

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RUPTURE of a corpus luteum is a not uncommon cause of hemoperitoneum but accurate preoperative diagnoses of this condition, even in uncomplicated cases, are infrequent.

Various authors have reported rupture of a corpus luteum subsequent to an abdominal blow, during sleep, coitus, bimanual pelvic examination, and the performance of ordinary activity.[1] A search of the medical literature has not revealed a case of rupture following vaginal surgery.

The seriousness of this postoperative complication serves dramatically to re-emphasize mandatory, direct, visual inspection of the uterine adnexal organs—the ovaries in particular—at the time of vaginal hysterectomy. The advisability of resecting a corpus luteum or corpus luteum cyst, should one be encountered at the time of hysterectomy, must also be strongly considered.

Case Report

Mrs. E. C. (OMH No. 8203), a 33-year-old white woman, para iv, gravida iv, was referred to the Oneida Maternity Hospital March 11, 1952, because of complete uterine prolapse of one year's duration. Her last child was born at term in February, 1951, 13 months prior to this admission. She had had no menstrual periods since delivery, and the procidentia occurred 1 month post partum. Otherwise her past medical, surgical, and obstetrical history was not revealing.

Her general physical examination was unremarkable. The breasts were moderately engorged and showed terminal lactation; the heart and lungs showed no pathological changes. There were no palpable abdominal viscera, nor was there any tenderness. Blood pressure was 128/70. The red blood cell count was 4.32 million, hemoglobin 12.75 Gm., and the white blood cell count and differential were normal.

Pelvic examination revealed complete uterine prolapse. The cervix was severely lacerated, ulcerated, and chronically inflamed, the corpus small, firm, and entirely external to the introitus. Downward projections of the anterior and posterior vaginal walls were associated with a cystocele and rectocele, both large. Reduction of the protruding mass was accomplished with ease, and rectal-vaginal-abdominal examination revealed no palpable organs or masses in the adnexal regions.

Preoperative, preparatory therapy consisted of an inflated ring "doughnut" pessary for temporary reduction of the procidentia, potassium permanganate douches twice daily, 5 c.c. of penicillin ointment to the cervix by vaginal applicator nightly, and Combisul, 1 Gm. orally three times daily.

On March 22, 1952, a vaginal hysterectomy, radical repair of cystocele, repair of rectocele and perineorrhaphy were done under Pontocaine spinal anesthesia. The operative procedure was without incident except for a small, accidental perforation of the urinary bladder that was immediately repaired with two inverting purse-string sutures of chromic 00 catgut suture. All major arteries—notably the uterine arteries and utero-ovarian anastomoses—were doubly ligated with chromic 0 catgut suture. The uterine adnexal organs were palpated and considered to be free of disease. Finally, a small Penrose drain was placed in the peritoneal cavity through the vaginal cuff, a 5 c.c. Foley bag retention catheter inserted into the bladder, and the vagina firmly packed with 2 in. gauze. During

surgery, the patient's blood pressure remained stable at 100/60, blood loss was minimal—estimated at 200 c.c., and the patient was returned to the ward in good condition after an operative procedure of 1 hour and 35 minutes' duration.

Postoperatively the patient's condition remained good: hourly blood pressure determinations were 100/60. She had received 1,000 c.c. 5 per cent glucose in distilled water intravenously, and vaginal bleeding was slight.

At 1:00 P.M., on March 22, 1952, approximately 3½ hours after completion of the operation, the patient's blood pressure fell to 70/50; pulse was 108 per minute and vaginal bleeding minimal. Treatment at this time consisted of 1,000 c.c. of 5 per cent glucose in distilled water with 2 c.c. of Levophed given intravenously at the rate of 20 drops per minute. Sedation was also given. At 2:30 P.M. there was no change in the patient's condition; she was tranfused with 500 c.c. of whole blood and her blood pressure rose transiently to 140/80, only to fall to 66/40 at 4:30 P.M.

At 5:30 P.M. she began to complain of moderately severe, intermittent, right upper quadrant pain that was partially relieved by subcutaneous morphine sulfate, ⅙ gr. There were no signs of intraperitoneal hemorrhage; vaginal bleeding remained minimal. The patient was completely lucid in spite of her persistent hypotension. Under close observation her condition remained unchanged.

At 8:30 P.M. the patient was returned to the operating room. The vaginal pack was removed and found to be moderately saturated with blood. Vaginal-abdominal examination revealed no pelvic or cul-de-sac masses or fullness. The Penrose drain was removed and a uterine dressing forceps inserted to spread the vaginal cuff. Voluntary straining by the patient and firm external abdominal pressure failed to produce more than 5 c.c. of dark red blood. A Penrose drain was reinserted into the peritoneal cavity and the vagina was again firmly packed with 2 in. gauze. The diagnosis at this time was vascular collapse, moderately severe, etiology unknown. We did not think at this time that laparotomy was indicated.

The patient was returned to her bed and a venoclysis of 1,000 c.c. of 5 per cent glucose with 2 c.c. of Levophed was begun. Her blood pressure became fairly stable at 100/50, and her pulse 128 per minute. Her general condition was fair. The intermittent, right upper quadrant pain persisted. Immediately after the infusion of glucose and Levophed was completed at 10:25 P.M., her blood pressure fell to 74/40. A hemoglobin determination at this time was 8 Gm., and the hematocrit was 25 c.c. of packed red cells per 100 c.c. of whole blood.

Almost simultaneously with the fall in blood pressure, profuse, bright red vaginal bleeding began, and a soft mass, arising from the pelvis and extending to the umbilicus, became palpable. The abdominal wall was flaccid: there was no direct or rebound abdominal tenderness. A diagnosis of hemoperitoneum and shock, secondary to hemorrhage from the operative site, was made, and the patient prepared for immediate laparotomy.

Under 1 per cent procaine hydrochloride infiltration of the abdominal wall and a 1:1,000 Pentothal Sodium infusion, the abdomen was entered through a 10 cm. lower midline incision. Approximately 1,500 c.c. of fresh and clotted blood was aspirated from the peritoneal cavity. Thorough inspection of the operative site revealed no source of bleeding. The right ovary, however, was the site of a 1.5 cm. hemorrhagic, cystic defect that contained a fresh blood clot. There was active bleeding from the periphery of this clot. A partial oophorectomy was done, and the ovarian wound closed with an atraumatic chromic 00 catgut suture. The operative site was packed with Gelfoam, and the abdominal wound closed in layers.

As a result of the partial ovarian resection and the transfusion of 1,250 c.c. of whole blood and 500 c.c. of irradiated human plasma during and after surgery, the patient's condition improved dramatically. Her blood pressure rose steadily from 64/50 to 130/90, her pulse slowed and became full and regular, and her skin warm and dry.

Convalescence from both the vaginal and abdominal surgery was uneventful, except for temperature elevations of 100.4° F. to 100.6° F., on the first, second, third, and fourth postoperative days. The patient was discharged as well on the ninth postoperative day.

Pathology Report.—The specimen consisted of a portion of the right ovary which measured approximately 2.5 by 2.5 by 1.5 cm. It was pale gray in color except for one area, measuring 1.25 by 0.5 cm., which was brown in color. On the cut surface there were noted two small, cystic areas filled with a clear, gelatinous material. Microscopic interpretation was hemorrhagic, cystic corpus luteum.

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PRIMARY OVARIAN PREGNANCY

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PRIMARY ovarian pregnancy is still a comparative rarity. Preston[1] found 84 proved cases of ovarian pregnancy in the literature and described an additional case of his own. Hertig[2] expressed the opinion that primary ovarian pregnancy comprises 0.7 to 1.07 per cent of all ectopic pregnancies. Its absolute incidence (based on 1 in 300 pregnancies being ectopic) is of the order of 1 for each 25,000 to 40,000 pregnancies. At Alta Bates Community Hospital, records are available for the years 1945 through 1951. During that time 14,011 patients delivered, 64 tubal pregnancies occurred (51 unruptured and 13 ruptured), and 1 primary ovarian pregnancy was encountered. The latter case is presented here.

M. G., a 20-year-old married woman, was examined for the first time on Aug. 10, 1951. The patient had been bleeding vaginally for 5 days with some lower abdominal cramps. The last menstrual period started June 15, 1951, and stopped as usual three days later. She had observed some breast fullness and nausea during the latter part of July. No previous pregnancies or menstrual irregularities had occurred. There had been no previous surgery. Pelvic examination at that time revealed a lemon-sized mass in the right lower quadrant, which the attending physician believed to be an ovarian cyst. Two weeks later, the patient was referred to me for consultation. A slight amount of vaginal bleeding had been noted daily, and breast fullness was still present. The patient had been ambulatory and free from abdominal discomfort.

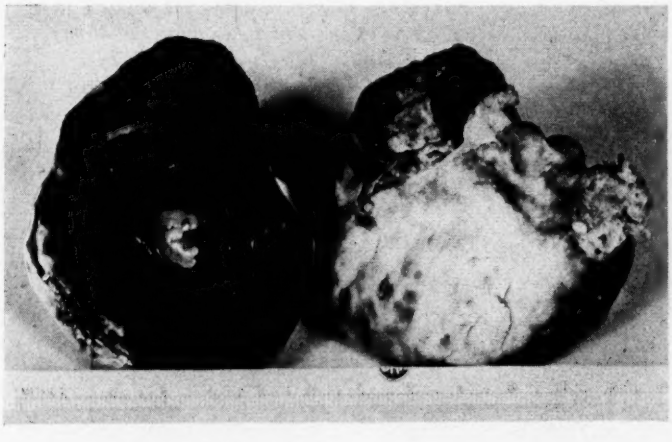

Fig. 1.

Physical Examination.—General physical examination revealed a very healthy, normal young woman in no discomfort and with normal pulse, temperature and respiratory rate. Breasts felt rather tense, and a suggestive pigmentation of nipples was present. Abdominal examination was negative for tenderness, scars, or masses. Pelvic findings disclosed a soft, nulliparous cervix. A normal-sized uterine fundus was palpable to the left of the midline and in an anterior position. A symmetrical, tender, firm mass approximately 6 cm. in diameter was palpable in the cul-de-sac, arising from the right adnexal region.

Laboratory Examination.—The hemoglobin was 15.5 Gm., erythrocyte count 4,650,000 per c.mm., leukocyte count 8,650 per c.mm., differential 40 neutrophils, 54 lymphocytes, 6 monocytes. Bleeding time was 3 minutes, blood type Moss II, A, Rh positive. Urine analysis was normal.

Preoperative Diagnosis.—Unruptured right tubal pregnancy.

Operation.—Dilatation and curettage, right salpingo-oophorectomy.

Operative Findings.—Dilatation and curettage were performed, the uterus being 3 in. in depth, uterine cavity normal in size. No tissue was obtainable with a sharp curette. At laparotomy there was no free blood in the peritoneal cavity. There were no intestinal adhesions. Visualization of the pelvic organs was accomplished with no difficulty, revealing a 5 to 6 cm. mass in the cul-de-sac, extending to the right adnexal area. The mass was hemorrhagic in appearance and appeared to be on the verge of rupturing. The mass was free from adhesions and was entirely confined to the ovary. The overlying right tube was normal in appearance. The fimbriated end of the right tube was normal. The left tube and ovary were normal in all respects. The uterine fundus was normal in size, in an anterior position somewhat to the left of the midline.

*Pathology Report.**—

Macroscopic Report.—The specimen consisted of an ovary with tube. The ovary measures about 7 by 5½ by 4 cm. The surface was pale but contained several dark, mottled areas. Cut section through the ovary revealed a central cavity measuring about 3 to 3½ cm. in diameter lined by a smooth membrane and containing a fetus which measured 1½ cm. in length. This cavity was surrounded by ovarian tissue which varies in thickness from 1 to 2 cm. in diameter. The fetus was attached to the inner lining of the cystic cavity by an intact umbilical cord. Most of the ovarian tissue was hemorrhagic, and only a thin layer of normal ovarian tissue was present on the surface. This ovarian tissue contained a small corpus luteum. The tube was attached to the ovary and measured about 4½ cm. in length. The fimbria was free, and the wall of the tube appeared grossly normal. The tube was entirely uninvolved in this pregnancy.

Microscopic Report.—Sections of the ovary showed the cavity to be filled with blood clot within which there were a number of chorionic villi. The ovarian stroma was infiltrated with a number of lymphocytes. The Fallopian tube showed a moderate amount of edema with some increase in height of lining epithelium.

Pathology Diagnosis.—Primary ovarian pregnancy.

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FIFTEEN-YEAR STERILITY DUE TO PITUITARY ADENOMA RELIEVED BY X-RAY THERAPY

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MRS. E. S., a white married woman, aged 34 years, was referred on April 1, 1946, for x-ray therapy because of difficulty in vision of the right eye.

She was American born and had been quite healthy in youth except for a nervous "twitch." Menstruation began at the age of 13 years and was regular until the age of 25, when, following a trip to Bermuda during which she was quite seasick, menstruation stopped and she had menstruated but 3 times since that time in 1937.

She wore "rest" glasses for ten or eleven years before marriage, which took place at the age of 27, but following which she seemed no longer to need them. For the past few years, however, she again noted some indistinct vision.

Six months before April, 1946, that is, about November, 1945, she noticed indistinct blurring of vision, worse on the right side. The condition persisted and in January, 1946, she sought medical advice and was referred to an ophthalmologist. The eye examination revealed the visual condition to be as follows: right eye, 10/200, absolute central scotoma, peripheral fields normal; left eye, 20/20, field normal.

The condition at first was believed to be a retrobulbar neuritis, and was treated as such for six weeks. No relief, however, followed, and the patient was referred to the neurosurgeon for consultation. A roentgenograph of the skull at this time revealed an enlargement of the pituitary. There also was slight enlargement of the feet, some headaches, sacroiliac pains, and occasional griping pains in the abdomen, and the patient had a distinct lisp in speaking. A diagnosis of pituitary tumor was made. X-ray therapy was recommended.

Upon examination at the beginning of the x-ray treatment, on April 1, 1946, the patient was a well-developed woman, exhibiting slight conversion of the left eye, widened pupil of the right eye, and a slight facial twitch on the right side. The patient lisped on talking and the tongue was thickened. A roentgenograph at this time showed an enlarged sella turcica with destruction of the posterior clinoid. No other abnormality was noted and her general health was good. Gynecologic examination revealed no pelvic abnormality.

High voltage x-ray was administered through a central forehead and right and left temporal areas with the x-ray directed toward the pituitary. A dose of 2,500 r (measured in air) was administered to the central and 2,000 r each to the right and left temporal areas. Treatment was administered between April 1 and 26, 1946. Headache and epidermitis followed treatment but by June 20, 1946, the ophthalmologist reported the patient very much relieved and with definite recovery of eyesight. At this time the ophthalmologist reported, "right eye vision gradually improved, the absolute central scotoma became relative and then disappeared so that the present right eye status is as follows: vision 20/40: there is no central scotoma but a small sector-shaped defect is present in the right temporal field. The left eye has remained normal throughout in all respects."

On May 13, 1950, the patient wrote that menstruation which had ceased at the age of 25 again occurred May 6, 1950, or at the age of 38. Her vision was practically normal.

On Jan. 2, 1952, the patient reported that for the previous two years her menstruation was regular and normal and that she was, in January, 1952, in the sixth month of pregnancy. Although she had been married for 13 years she had never previously been pregnant.

On March 13, 1952, at the age of 40 years, Mrs. E. S. gave birth to a normal baby girl.

Summary

A married woman, aged 34 years, suffered visionary disturbances due to a pituitary tumor. Following x-ray therapy the tumor receded, vision was restored, and the amenorrhea and sterility which had existed for 13 years were relieved, and at the age of 40 she gave birth to a normal baby girl, demonstrating the value of x-ray therapy in the treatment of pituitary tumors and amenorrhea and sterility.

755 PARK AVENUE.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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PRIMARY adenocarcinoma of the Fallopian tube is the rarest of all gynecological cancer, its incidence being about 0.3 per cent of all genital cancers.[1] Since the first case reported by Raymond in 1847,[2] there have been 487 cases in the literature. Within the past 17 years only 85 cases have been reported.

The age incidence is similar to that in corpus carcinoma, between 40 and 60 years of age; the youngest patient was 18 and the oldest was 80. It is extremely rare in the Negro population. Three cases have been reported with a double primary lesion, the second primary lesion being in the breast in all three cases.[3]

In 70 per cent of the cases, the neoplasm occurs in the outer portion of the tube. When it arises at the isthmus, the prognosis seems to be poorer. Wechsler, in reviewing the literature in 1926, found an equal incidence between the left and right tubes.[4] However, Corscaden claims 95 per cent are unilateral with a higher incidence on the right side.[1]

Most writers feel that there is no association between the degree of histological malignancy and prognosis. Hu and associates[2] found a correlation in that 7 cases were classified as Grades 1 and 2. Six of these patients are living and well 1½ to 28 years later. Six patients with Grade 3 died 5 to 27 months later.

A. P., No. 50-7580, a 66-year-old white practical nurse, was admitted to the Flushing Hospital on July 3, 1950, from the outpatient department with a chief complaint of vaginal bleeding.

The patient had her menopause 20 years previously (age 46). Since that time she had been well until one month prior to admission, when she noticed some slight pink staining, intermittent in nature and gradually increasing to a bloody discharge. There was no pain, no watery discharge, no loss of weight, no anorexia. As a matter of fact, the patient had gained 20 pounds during the past year. She had no urinary complaints.

Past History.—She was para ii, gravida ii, with children 37 and 40 years old. She had no previous operations. Menarche was at the age of 14. Menses were always regular, with approximately 30 day cycles, the flow lasting from 4 to 5 days.

Physical Examination.—The patient was a well-developed, well-nourished obese white woman with a blood pressure of 160/100. Her general physical examination was within normal limits. Pelvic examination revealed an atrophic vagina with good support of its walls. The cervix was small, clean, atrophic, nontender and in the axis of the vagina. The corpus was not enlarged, was anterior and in the midline. No adnexal masses were palpated.

The erythrocyte sedimentation rate was 32 mm. in 1 hour. Red blood count was 5,110,000 per cubic millimeter. Hemoglobin was 14.5 Gm. Blood was Type A, rh positive. The urine analysis was normal. A Papanicolaou smear revealed only a few clumps of desquamated basal cells concomitant with the senile changes in the genital tract. No abnormal cells were seen.

Examination Under Anesthesia.—This revealed the same pelvic findings as on admission. The diagnostic curettage provided extremely scant curettings, which grossly appeared as atrophic endometrium. There was a mass, about at the level of the pelvic inlet, approximately 5 by 6 cm., firm, fixed, and irregular in shape, which could be palpated. The pathological report was myometrium with a few atrophic endometrial glands.

A laparotomy was performed on July 12, 1950, with a preoperative diagnosis of fibromyomas or possible ovarian neoplasm. The operative procedure consisted of a total hysterectomy and bilateral salpingo-oophorectomy.

Operative Findings.—The uterus was small and atrophic. The right tube and ovary were atrophic. The left tube and ovary were incorporated into a friable mass of tissue which was adherent to the posterior surface of the uterus, the cul-de-sac, the rectum, and the left ureter.

Postoperative Diagnosis.—Probable carcinoma of the left ovary.

Pathological Diagnosis.—

Gross: The specimen consisted of the uterus removed in toto with both of its adnexa. The uterus was atrophic, measuring 72 by 52 mm. The right tube was 55 mm. in length, its lumen was easily probed. The right ovary was 22 by 10 by 7 mm., its capsule was thick and parenchyma fibrotic. The left tube was 72 mm. in length. At its fimbrial end there was a firm nodular growth measuring 35 by 34 by 26 mm. Multiple sections of this nodule revealed a finely granular surface ranging from gray white to yellow in color. At one area it was seen to connect with the lining of the tube. A separate segment of the above described tumor tissue measuring 42 by 32 by 14 mm. was also submitted. The left ovary measured 25 by 10 by 8 mm. and fibrotic.

Microscopic: The uterine musculature showed senile fibrosis. The endometrium was atrophic with evidence of recent curettage and chronic cervicitis was noted. The left ovary, right ovary, and right tube were fibrotic. The left tube revealed a chronic salpingitis and primary adenocarcinoma. The carcinoma cells were in an alveolar and medullary pattern. Individual cells were undifferentiated, many of their nuclei were undergoing mitosis, and the cytoplasm was vacuolated. Several areas showed the malignant cells continuous with the normal tubal epithelium. Diagnosis was primary adenocarcinoma of the left Fallopian tube, Grade 3.

The patient had an uneventful postoperative recovery and was discharged from the hospital on the seventh postoperative day. She received postoperative radiation through 4 pelvic portals for a total of 1,800 r through each port.

Follow-up.—The patient is now 23 months postoperative, alive, well, and gaining weight. She has no complaint whatsoever. There are no local nor distant metastases clinically evident.

Comment

1. This is approximately the four hundred eighty-eighth case reported in the world literature.

2. All three criteria for diagnosis are fulfilled, i.e., grossly, the main tumor was in the tube, the mucosa was involved showing a papillary pattern, and a transition between benign and malignant epithelium was demonstrable.

3. Despite the operative findings and microscopic anaplasia, our patient is alive and well 23 months postoperatively.

4. The extreme difficulty in preoperative diagnosis and even at the operating table is responsible for this lesion being frequently overlooked.

5. The surgeon should open the specimen at the operating table, keeping in mind that Fallopian tubes showing chronic salpingitis may have complications of a more serious type of disease, thus avoiding an incomplete operation.

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BILATERAL BRENNER TUMORS OF THE OVARIES

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ORTHMAN[1] described what was probably the first reported case of a Brenner tumor of the ovary. Eight years later, in 1907, Brenner[2] described three such cases, at which time he termed the tumor "oophoroma folliculare," because he believed the source to be the follicle. In 1932 Robert Meyer[3] more clearly defined and classified these ovarian tumors. He believed that they arose from Walthard's inclusions, and were not granulosa-cell growths. On the other hand, Schiller[4] pointed out that in some instances these tumors may arise from Wolffian epoophoron tubules which are included in the ovarian hilum and which may form epithelium like that normally found in the urinary tract. Johnson and Dockerty[5] mention a third hypothesis pertaining to the origin of these tumors, namely, that they may be of teratomatous origin based on the fact that about one-third of Brenner tumors occur in the walls of mucinous cysts of the ovary. A mucinous cyst so frequently is part of a dermoid cyst that many investigators consider it to be a teratoma with overgrowth of mucous glands to the exclusion of other elements. However, Meyer's theory is still the one most widely accepted.

The Brenner tumor is slow growing and considered to be a benign lesion. Over 50 per cent occur beyond the age of 50 years. It comprises 2 per cent of all solid ovarian tumors, which in turn comprise only 20 per cent of all ovarian tumors. Seventy per cent of the Brenner tumors are solid, while thirty per cent are present in the wall of a cyst, usually a pseudomucinous cystadenoma. It is usually unilateral, but it may be bilateral. In 1942 Fox[6] reviewed the literature and found that among 170 cases of Brenner tumor there were only 13 cases (7.6 per cent) in which the growth was bilateral. Johnson and Dockerty[5] reported the fourteenth case of bilateral Brenner tumor in 1945.

The Brenner tumor produces no hormonal disturbances of the endometrium and no characteristic symptoms so that it is usually found incidentally at operation or autopsy. The size of the tumor varies between a few millimeters to several centimeters, the largest recorded being 15 pounds, as reported by Neiman.[7] Grossly, the solid form has the appearance of a fibroma, the cut surface however, presenting a yellowish tint. Hemorrhage and necrosis are rare findings.

Microscopically, the chief danger is in mistaking the Brenner tumor for a primary or metastatic epithelioma. However, the predominantly fibrous nature of the growth, the striking uniformity of the cells and the complete absence of mitosis help to differentiate it from a malignancy. Two features appear to be necessary for a diagnosis, namely, the characteristic nests of epithelial cells, which resemble squamous cells, although they do not possess intercellular bridges or keratin and a fibromatous connective tissue stroma surrounding the epithelial nests.

The patient was a 35-year-old white woman, para ii, gravida ii, who was first seen on Jan. 25, 1952, complaining of a dragging sensation in the lower pelvis for several years, low backache for several weeks, and severe urinary stress incontinence. There were no menstrual alterations. She had had an appendectomy at the age of 16 and a Sturmdorf cervical amputation for chronic cervicitis 13 years ago. Family history was essentially noncontributory.

Physical findings were essentially normal except for the following: The thyroid isthmus was palpable and smooth. She exhibited fine tremors of the fingers of the hands.

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Basal metabolic rate was plus 13. Examination of the heart revealed a soft systolic blow at the apex. On pelvic examination the external genitals were negative. She presented a urethrocele, a third-degree cystocele, a second-degree rectocele, an enterocele, and a second-degree uterine descensus. The uterine fundus was anterior, normal in size, mobile, and smooth. The left ovary was palpable and slightly irregular, but not enlarged. The right ovary was palpated in the posterior cul-de-sac, was enlarged to about 4 by 5 cm., was hard, irregular, tender, and freely mobile.

On Jan. 29, 1952, she underwent a vaginal hysterectomy, an anterior and posterior colporrhaphy, a urethral plication, and repair of the enterocele. At operation both ovaries and tubes were visualized. The right ovary was enlarged to about 4 by 5 cm., and was hard and irregular. A right salpingo-oophorectomy was performed. On cut section the tumor mass was solid and had a yellowish tint. Immediate frozen section revealed a Brenner tumor of the ovary. The left ovary was not enlarged but was irregular and presented a hard mass in the upper pole which measured 2 cm. in size. This mass was enucleated in order to conserve the remaining ovarian tissue. On microscopic examination this mass was also a Brenner tumor of the ovary.

The patient was discharged from the hospital on Feb. 7, 1952, after an uneventful postoperative course.

Summary

A total of fourteen cases of bilateral Brenner tumor of the ovary have been reported. An additional case has been presented.

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A SAFE INSTRUMENT FOR DILATING A CERVICAL STRICTURE

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(From the Shelton Clinic)

INTRODUCING a sound into the normal cervix is a relatively simple office procedure, but the unyielding stenotic cervix can resist the efforts and tax the ingenuity of the surgeon. Flexible probes may bend and rigid probes may establish false passages with perforation of the uterus. Ten years ago, having exhausted the supply of conventional probes and available dilators, I discovered an instrument that has proved both successful and safe for penetration of the stenotic cervix.

The instrument used is not a new one and is available in nearly every surgery. It is the 6 in. grooved director which has a flexible olive tip (Fig. 1). The tongue-tie shield lends itself well to use as a small handle to be grasped between the operator's thumb and index finger. The 6 in. director has a more delicate probe tip than the 8 in. director and is more satisfactory for a stenotic "pin-point" cervical os. However, the latter instrument by virtue of the longer shaft and greater diameter is convenient when the stenosis is less severe. If the flexible tip is bent slightly toward the open side of the V, the director will more readily follow the contour of the uterine canal. The gradually enlarging V of the grooved director diminishes the possibility of perforation of the uterus and provides three dull cutting edges which pierce the stricture at 10, 2, and 6 o'clock. Immediately after penetration of the cervix by the grooved director, a Simpson uterine sound can readily be passed followed by further dilatation as necessary.

Fig. 1.

The conventional 6 in. grooved director with a flexible olive tip is a safer and more satisfactory probe than the flexible or rigid probe in the dilatation of a stenotic cervix because it helps to eliminate the possibility of perforation of the uterus and dilates the stenotic cervix sufficiently to allow passage of sounds. The use of this grooved director is an aid in preparing the stenotic cervix for such office procedures as endometrial biopsy and uterotubal insufflation.

921 WESTWOOD BOULEVARD

Department of Reviews and Abstracts

Selected Abstracts

Anesthesia, Analgesia

Davis, M. Edward, Andros, George J., and King, Albert G.: Use of Methadone-Scopolamine in Obstetric Analgesia, J. A. M. A. 148: 1193, 1952.

On the basis of experience the authors felt that a combination of 10 mg. of methadone hydrochloride and 0.4 to 0.5 mg. of scopolamine hydrobromide administered subcutaneously held greatest promise as a satisfactory method for producing analgesia-amnesia in the laboring woman. It was noted that 64 per cent of primiparas and 62 per cent of multiparas were maintained in a comfortable state during contractions by methadone and scopolamine. Moderate restlessness was noted in 22 per cent of both multiparas and primiparas, while 16 per cent and 14 per cent, respectively, were severely restless with each pain. The use of methadone and scopolamine in average therapeutic amounts (usually one dose) does not prolong labor. Respiratory depression of the infants is no more striking than with other narcotics. As is true with other narcotics, the greatest fetal respiratory effect is noted when methadone is administered 90 or 120 to 210 minutes prior to delivery. A premature infant, or a mature fetus exposed to trauma or anoxia in labor should in particular be spared the additional depressing effect of the combined use of barbiturates, a narcotic, and deep inhalation anesthesia.

WILLIAM BERMAN

Gomez, Romero C.: Obstetrical Analgesia With Trilene, Acta ginec., Madrid 2: 563, 1951.

The author reviews the extensive experience in England with trichlorethylene (Trilene), then gives his own experience. He is enthusiastic about this method of analgesia, which is particularly applicable to the second stage of labor. It is simple and cheap to use, is devoid of danger for mother or child, does not prolong parturition, maintains the cooperation of the patient, does not increase the incidence of operative delivery, and does not interfere with the normalcy of the third stage of labor.

The author insists upon the necessity of proper technique if good results are to be obtained. The patient must be familiarized with the use of the apparatus; this can be done either before the onset of labor or during the early stages of labor. Analgesia by other agents is used during the first stage of labor if necessary, although there is no objection to using Trilene when dilatation of the cervix is well advanced. It is rarely necessary to use Trilene for more than five or six hours, although it has been used for periods up to ten hours without ill effects.

The parturient must begin the inhalation at the very onset of each contraction, and inhale deeply and repeatedly before the contraction reaches its peak; in this manner she will have analgesia when it is needed, whereas if she waits until the contraction is painful before beginning the inhalation, analgesia will occur after the acme of the pain has passed, when it is no longer needed. Good technique is, therefore, extremely important. No complications incident to this method have been encountered.

MAGIN SAGARRA

Cancer, Malignancies

Nogales, Ortiz F.: Tuberculosis and Carcinoma of the Cervix, Acta ginec., Madrid 2: 143, 1951.

The author, associated with the Obstetric and Gynecologic Division of the Madrid Medical School, reports a case of coexistent carcinoma of the cervix with tuberculosis of the cervix and endometrium. The patient was a nulliparous woman, 20 years of age, whose menarche was at 14 years of age. Her cycle was every 26 days, 4 to 5 day type. She gave a history of pleurisy of three years' duration and of two painful worm infestations in the right iliac fossa subsequently. Initial pelvic examination revealed a normal-sized uterus with an orange-sized mass in the left adnexal area. There was contact bleeding upon examination of the cervix. Biopsies from the portio and curettings from the uterine cavity revealed the coexistent diseases. Four photomicrographs illustrate the principal findings. The clinical grade of carcinoma was not mentioned.

The author summarizes his own and discusses seven similar cases collected from the literature exhibiting this rare association of tuberculosis and carcinoma of the cervix. He notes that treatment includes preliminary or complemental treatment with para-aminosalicylic and streptomycin with radiation therapy and surgery utilized subsequently.

CLAIR E. FOLSOME

Weinstein, L., Aycock, W. L., and Feemster, R. F.: The Relation of Sex, Pregnancy, and Menstruation to Susceptibility in Poliomyelitis, New England J. Med. 245: 54, 1951.

Observations here reported show that sex, menstruation, and the pregnant state may play an important role in the pathogenesis of clinical poliomyelitis. Whereas in childhood more boys than girls are hospitalized for the disease, after the age of twenty this relationship is reversed. Seventy-eight per cent of the adult female poliomyelitis patients had menstrual periods from five days before, to four days after the beginning of the illness, which suggests that endocrine factors provoke or hasten central nervous system invasion. Similarly, it was found that the coexistence of pregnancy was threefold the normal rate for the age group involved. The exact role of the pregnant state in increasing susceptibility is not known. Endocrine changes may aggravate the manifestations, thus converting a subclinical state into a clinical disease. If delivery takes place during the acute phase of poliomyelitis, there is usually an increase in the severity of the paralysis, or extension of involvement to muscles previously unaffected.

IRVING L. FRANK

Gilliam, A. G.: Fertility and Cancer of the Breast and of the Uterine Cervix. Comparisons Between Rates of Pregnancy in Women With Cancer at These and Other Sites, J. Nat. Cancer Inst. 12: 287, 1951.

The author has carried out comprehensive statistical analysis of the marriage and pregnancy records of 2,497 women with cancer of the breast, cervix, other genital organs, skin, and gastrointestinal tract. The role of such independent variables as age, color, sex, religion, type of contraception, illegitimacy, and place of residence is evaluated by cross-comparison in an effort to isolate factors of possible etiological importance in the above-listed lesions.

This study supports the view that marriage and childbirth reduce a woman's chance of developing cancer of the breast, and increase her risk of cancer of the cervix. If, however, childbearing affords some protection against cancer of the breast, these data suggest that it may be ineffective after age 30. Similarly, if childbearing is etiologically important in cervical cancer, this effect seems to be lost after age 25. A hitherto unsuspected relationship was the correlation between fertility and cancer of the skin, which was higher than any other.

IRVING L. FRANK

Endocrinology

Fried, P. H., and Rakoff, A. E.: The Effect of Chorionic Gonadotropin and Prolactin on the Maintenance of Corpus Luteum Function, J. Clin. Endocrinol. **12**: 321, 1952.

During recent years, considerable importance has been attached to dysfunction of the corpus luteum in certain types of sterility, in menorrhagia and in habitual abortion. This was attributed, not to basic functional or anatomical changes in the corpus luteum itself, but to a deficiency of the pituitary luteotropic mechanism. In the past, therapy of such conditions with chorionic gonadotropin, except where very large doses (20,000 I. U.) were given daily, was most disappointing. These studies of chorionic gonadotropin have been paralleled more recently by investigations of the luteotropic properties of pituitary lactogenic hormone. It has been shown that this hormone has similar properties of maintaining the function of the corpus luteum, but results were not consistent, and many cases of deficient progesterone production were not benefited by its use.

The authors have postulated a theory that both the chorionic gonatropin and the lactogenic hormone are necessary for lutein function, since they felt that a synergistic relationship between these substances was present. They have carefully studied 12 patients including sterile women, normally menstruating women, castrates, and women with hypomenorrhea and menorrhagia over periods of several months of combined therapy. These cases were followed by means of endometrial biopsies, urinary pregnanediol excretion determinations, and daily basal temperature records through several menstrual cycles. These tests were used because it was felt that the endometrium mirrored the corpus-luteum effect, and the basal temperature curves provided day-to-day evidence of corpus-luteum function.

The hormones used in this study consisted of sheep lactogenic hormone (Luteotrophin) and chorionic gonadotropin (Follutein or A.P.L.). It was found that the minimal effective combination that caused prolongation of corpus luteum function was 2,000 I. U. of chorionic gonadotropin and 200 units of lactogenic hormone. These dosages were approximately one-tenth of the dosage necessary when either drug is used alone. When the injections were started within a week of the ovulatory temperature rise, and given three times weekly, it was found that because of the luteinizing effect the postovulatory phase was prolonged in regularly menstruating women up to 13 days. After this period, regardless of injection therapy, menstruation occurred. The authors interpret this to be due to the inability of the stimulating hormones to whip a dying corpus luteum. During this time the basal temperature remained high, the endometrial biopsies showed normal secretory endometrium, and urinary pregnandiol levels were maintained. Therapy started during the preovulatory phase did not affect ovulation. Furthermore, if therapy was started during the time of corpus luteum regression, no effect was noted, showing that an old corpus luteum cannot be revived. Changes in the cycle were noted only during the period that the injections were given and were not carried over into subsequent cycles. However, production of antihormone to the lactogenic hormone was noted after three months of successive therapy. No local or general toxic effects occurred as the result of injections. On the basis of these findings the authors believe that prolactin and chorionic gonadotropin act synergistically, and that the combination has a definite place in the armamentarium of the physician in the treatment of abortion due to faulty implantation; to short life of the corpus luteum; or to corpus luteum failure before placental secretion can take over. It may also be indicated in certain cases of menstrual dysfunction and sterility. This study offers, moreover, some evidence for postulating the transformation of the corpus luteum of the menstrual cycle into the corpus luteum of pregnancy and its maintenance during the first trimester of pregnancy by the chorionic gonadotropin of the trophoblast.

L. B. WINKELSTEIN

Gynecology

Preston, P. G.: A Review of 100 Cases of Transplantation of the Ureters in the Treatment of Obstetrical Vesicovaginal Fistula, J. Obst. & Gynaec. Brit. Emp. **58**: 282, 1951.

Transplantation of the ureters was done in 100 African native women with vesicovaginal fistula. Indications for the operation were: a fistula large enough to admit one finger; a vesicocervical fistula; or marked fibrosis of the vaginal wall. In these cases transplantation of both ureters into the pelvic colon was done in one stage by the technique described by Grey Turner and others, except that no drain was inserted in the ureter. The first 35 patients in this series were operated on in an out-station (''bush hospital''), where blood urea estimations could not be made. In all other cases, if blood urea was over 40 mg. per cent, operation was not done until it had been diminished by adequate treatment. Every patient was admitted to the hospital at least seven days before operation and given potassium citrate mixture and a sulfonamide; three or four days before operation proseptazine (1 Gm. three times a day) was given because it is more effective against *Bacillus faecalis* and *Bacillus coli* than the sulfonamides. A sulfonamide drug was also given for three days after operation. Anuria often persisted for twenty-four hours after operation; if it persisted after that time a continuous intravenous drip of 4.45 per cent sodium sulfate solution was given. There were 21 postoperative deaths, the chief causes of which were peritonitis, hypostatic pneumonia, and pyelitis and pyelonephritis; while this mortality rate is high, it compares favorably with that reported by Murray and Ahmed in 1943. Hospital and nursing facilities are often inadequate in African hospitals. Eleven patients have died since operation; in 2 cases death occurred during childbirth; the exact cause of death could not be ascertained in most instances, but in at least 6 cases death could not be attributed to the operation. All the surviving patients are relieved of their urinary incontinence. In most cases these large vesicovaginal fistulas requiring transplantation of the ureters in African women were due to prolonged labor of three or more days. The only way in which the incidence of these fistulas can be reduced is for the women to seek the help of European antenatal and obstetrical services.

HARVEY B. MATTHEWS

White, Margaret Moore: Errors in Technique and Interpretation of Hysterosalpingography and Tubal Insufflation, J. Obst. & Gynaec. Brit. Emp. **58**: 573, 1951.

From experience in over 6,750 cases in which tubal insufflation or hysterosalpingography was done to determine tubal patency, the author emphasizes the following points in technique, failure to observe which may lead to error in the diagnosis: A preliminary roentgenogram of the pelvis should be made, especially if the patient has had a previous salpingogram. A cannula should be used that is suitable for each case, and its patency should be tested. The opaque medium should be warmed, as this renders a heavy oil medium more penetrable and reduces the danger of cornual spasm. If there is marked angulation of the cervix, a vulsella should be affixed to the cervix to alter the position of the uterus and tubes. The opaque medium should not be allowed to escape from the cervix until two or three minutes after radiograms have been taken. If the introduction of the opaque medium is not controlled radiographically, too great pressure on the syringe should be avoided. An oily opaque medium should not be used if there is evidence of previous infection or if the kymographic tracing has indicated tubal stenosis. A sufficient amount of opaque medium should be used, and a number of films taken in each case. A second salpingography should be done if the diagnosis is uncertain. In the interpretation of the findings on tubal insufflation, intestinal borborygmi may be mistaken for escape of the gas from the tube; the sound of gas bubbling through a hydrosalpinx or a tube with the fimbriated end occluded may also be mistaken for escape of the gas into the peritoneal cavity; or the sound of gas escaping from the cervix may be mistaken for gas escaping from the tubes. These mistakes are best avoided if the operator uses the stethoscope himself for auscultation of the abdomen. In the interpretation of the

kymographic tracing, the possibility of spasm must always be considered, and the significance of variations from normal, such as no fluctuations or poor fluctuations under normal or increased pressure, must be carefully interpreted. In the study and interpretation of the hysterosalpingogram, careful assessment of the size of the uterus and any irregularities of its contours must be made. Details of the length, caliber, tortuosity, and irregular filling of the tubes must be noted and the findings compared with clinical findings and the kymographic tracing. Opaque medium still in the tubes and other pelvic shadows must not be misinterpreted as peritoneal spill, and the localized "pockets" of peritoneal spill must be recognized. The preliminary x-ray study of the pelvis is of value in avoiding some of these errors of interpretation of the hysterosalpingogram.

HARRY B. MATTHEWS

Zondek, B., Bromberg, Y. M., and Rozin, S.: An Anterior Pituitary Hyperhormonotrophic Syndrome (Excessive Uterine Bleeding, Galactorrhoea, Hyperthyroidism), J. Obst. & Gynaec. Brit. Emp. **58**: 525, 1951.

In 280 cases of uterine bleeding due to hyperestrogenism, there were 5 cases in which the excessive bleeding was accompanied by galactorrhea and symptoms of thyrotoxicosis. The excessive uterine bleeding in these cases was of long duration; the uterine mucosa showed glandular cystic hyperplasia characteristic of hyperestrinism. The signs of hyperthyroidism were exophthalmos (marked in 2 cases, of lesser degree in 3 cases), sudden loss of weight, nervous symptoms, and increase in the basal metabolic rate. Galactorrhea was present in all cases, with a flow of milk from both breasts. In 3 cases there was a slight hypoglycemia, with a flat blood sugar curve in the glucose tolerance test; there was no hypersensitivity to insulin. Other secondary symptoms were fatigue, anemia, and sterility. This syndrome is attributed to hyperactivity of the anterior lobe of the pituitary, resulting in a hyperproduction of the gonadotrophic hormone (FSH) and also of the thyrotrophic and lactotrophic hormones, and possibly of the pancreatrophic hormone (in cases showing hypoglycemia).

HARVEY B. MATTHEWS

Labor, Management, Complications

Kobak, Alfred J., Fields, Charles, and Fitzgerald, James E.: Antibiotics and Low Cervical Cesarean Section in Dystocia or Intrapartum Sepsis, J. A. M. A. **148**: 1478, 1952.

The authors open their discussion with the frank statement that the low cervical section may be safely employed in the presence of sepsis. This statement is supported by 140 consecutive transperitoneal cesarean sections without a fatality in patients who were either infected or potentially infected. In cases of dystocia and with the application of antibacterial agents, a full test of labor can now be given without nullifying the safety of a transperitoneal cesarean section when it later becomes necessary. Regardless of the ultimate manner of delivery, the obstetrician must be mindful of keeping the patient in the best possible condition. It is important to combat dehydration and acidosis. Blood transfusions are an important adjunct to therapy. Abdominal delivery is decided upon when it is obvious that labor is not progressing.

Penicillin, the safest and most dependable antibiotic, is weak in counteracting the effects of the gram-negative intestinal group bacilli; therefore, it should be supplemented by sulfadiazine or streptomycin to increase the chances of recovery. Chloramphenicol may interfere with the action of penicillin and should be used cautiously.

WILLIAM BERMAN

Monckeberg, G.: Use of Dihydroergotamine in Obstetrics, Bol. Soc. chilena de obst. y ginec. **16**: 134, 1951.

Dihydroergotamine is a synthetic derivative of ergotamine by introduction of two hydrogen atoms. This drug, while being less toxic than ergotamine, has a more powerful

sympathicolytic or adrenolytic effect, as shown by Rothlin. The rationale for its use in obstetrics lies in its sympathicolytic effect which could theoretically relax the spastic or rigid uterine cervix. Ergotamine is contraindicated because of its direct oxytocic action on uterine muscle.

The author, after reviewing the encouraging results obtained by others, reports his own experience. The drug, in doses of 0.25 to 0.5 mg. intramuscularly or intravenously, increased the frequency of preexisting uterine contractions and appeared to have a definite relaxing effect on the cervix in most cases. The intensity and duration of contractions were not appreciably affected. These small doses did not initiate uterine contractions if they were not already present.

The author, after observing the above-described effects in 100 unselected cases, studied the action of the drug in the following types of cases:

1. Prolonged Labor.—All patients (9 primiparas and 11 multiparas) had been in labor over 24 hours, with cervical dilatation between 1 and 3 cm. About half of these patients received only one dose of 0.25 mg. of dihydroergotamine; the others received a second dose after a two-hour interval. When the response had been doubtful after the first dose, it was often dramatic after the second.

In most of these patients with prolonged labor the drug produced a marked increase in pain and uterine contractions together with cervical relaxation. The cervix dilated fully in 14 (70 per cent of cases) and failed to do so in 6 (30 per cent).

2. Acceleration of Labor.—Thirty patients (19 primiparas and 11 multiparas) were given 0.5 mg. intravenously for the purpose of accelerating labor. All responded effectively with increased uterine activity and rapid dilatation of the cervix.

3. Induction of Labor.—Ten cases were observed. All were given doses higher than 0.5 mg. No effect noted in 3 cases; 2 had intense uterine contractions and later were found to have retroplacental hematomas; 1 patient, after receiving three doses of 0.5 mg. at eight-hour intervals, developed a slight hypertonic state of the uterus shortly after the third injection, and the fetal heartbeat was lost (subsequent autopsy of the fetus revealed only asphyxia in utero); the remaining 4 patients were delivered within 24 hours after using the drug. In the light of these observations the author does not feel that dihydroergotamine is a satisfactory agent for the induction of labor.

4. Operative Delivery.—The idea of using dihydroergotamine for obstetrical maneuvers was based on the observation that the oxytocic action of the drug disappears under general anesthesia (or spinal anesthesia). This left the desirable sympathicolytic effect alone and suggested possible advantage in fetal extraction or internal version. The drug was used in 18 cases, in doses of 0.5 to 1 mg. intravenously with the patient under deep anesthesia with ether. Results were encouraging, with most of the maneuvers successfully completed.

From his experience with the use of dihydroergotamine the author concludes that the drug has a definite effect in increasing uterine contractions when these are already present. The drug has a large percentage of failure in dilating the cervix. Its use carries a significant risk in induction of labor. Further investigation is in order to evaluate its usefulness in operative delivery.

The author recommends doses of 0.5 mg. or more intravenously or intramuscularly in cases of advanced labor with over 5 or 6 cm. dilatation. These doses and the intravenous route are contraindicated if dilatation is 4 cm. or less.

Prolonged labor with cervical dystocia can be resolved in 70 per cent of cases by the use of dihydroergotamine in 0.25 mg. doses which can be repeated after 3 hours if necessary. Cervical dystocia fails to respond in 30 per cent of cases.

Secondary effects of dihydroergotamine on blood pressure and fetal heart are insignificant.

Hypophysin, ergotamine, or methergine may be used in the third stage of labor if indicated, there being no antagonism between these agents and dihydroergotamine.

MAGIN SAGARRA

Newborn

Campbell, W. A. B.: Purulent Parotitis in the Newborn, Lancet 2: 386, 1951.

In a spontaneously delivered infant suppurative parotitis developed six days after birth, the predominant organism being *Staphylococcus aureus.* After treatment with penicillin, sulfadimidine and streptomycin, followed by incision and drainage, recovery was uneventful.

Purulent parotitis in the newborn is a distinct clinical entity, differing from suppurative parotitis in other age groups in that it does not arise from intraoral infection. The exact etiology is not clear; the predominant organism is the *Staphylococcus aureus,* presumably blood borne. Local trauma at the site of delivery is a possible factor. Sanford and Shmigelsky (1945) collected 57 cases, an incidence of one in 2,000 births.

IRVING L. FRANK

Swinscow, Douglas: So-Called Accidental Mechanical Suffocation of Infants, Brit. M. J. 2: 1004, 1951.

A cautious evaluation of infant deaths in Wales and England as a result of suffocation is presented. The years included are 1921-1949 and the caution is necessary because of changes in classification during this time. Pathological study of cases ascribed to accidental suffocation indicates that the causes are much more probably disease. Although such studies do not enable one to estimate the proportion, a considerable number of the cases showed lesions sufficient to account for death. Chief among these were: acute nephritis, diseases of the ear and mastoid, enteritis, congenital heart disease, influenza, pneumonia, bronchitis, and meningitis.

Changes in death rates over the period of years examined are difficult to evaluate and are tabulated as occurring in bed, in a cot, due to food, and "other." The author notes a distinct postwar rise in deaths due to suffocation by food. He feels this may be influenced by a decline in breast feeding, babies being left alone to bottle feed, regurgitate, and inhale vomitus. Deaths in bed have had a tendency to decline, and again this might be due to more bottle feeding with the result that fewer mothers go to sleep while breast feeding and inadvertently suffocate their infants in bed. He notes an increase in death in cots, possibly influenced by higher wages, allowing parents to buy cots for the babies in preference to their sleeping in beds with other occupants.

Swinscow believes the importance of precisely determining the cause before attributing the death of a baby to accidental suffocation lies in the effect that such a diagnosis may have on the parents; no such diagnosis should be made unless there is clear evidence of it.

JOHN T. COLE

Lenoir, A.: Radiologic Signs of Fetal Maturity, Gynaecologia 133: 98, 1952.

The age and the maturity of the fetus in utero can be determined by certain radiographic signs. Although these signs are not 100 per cent accurate, they can, when integrated with other factors, be a valuable aid in such a diagnosis. The procedure is entirely without harm to either the mother or the child. It has been calculated that it would be necessary to make more than 60 such radiologic examinations over a short period of time to produce a single erythema dose for the mother. Furthermore, after the fifth month of gestation, the amount of deep radiation received by the fetus is insignificant. If one is concerned by the possible production of mutants by this small amount of radiation, experiments conducted on many generations of Drosophila flies show such concern to be without foundation.

Three important points are evaluated by x-ray in the determination of fetal age: (1) the position of the fetus; (2) fetal mensuration; and (3) fetal centers of ossification. As to the position or attitude of the fetus, the author feels that this is of significance only in cephalic or breech presentations. In all other presentations it is of no value. Signs of maturity include the degree of flexion of the head, the relation of the position of the chin to the chest

wall, the crossing of the arms, and the flexion of the knees on the abdomen. As for the measurements of the fetus, all basic diameters of the head and certain lengths of the spine and long bones are of value. However, the variations in the normal due to many extrinsic factors are very great, and cannot be utilized with absolute assurance. The third factor mentioned, that of the presence or absence of ossification centers, is of prime importance, not only for the determination of maturity of the fetus, but also for the accurate diagnosis of fetal age before term. For example, the author finds that evidence of ossification of the semicircular canals is present at the twentieth week of gestation; of the temporal bone at the twenty-fourth week; of the calcaneous at 6 months; of the astragalus at 8 months, and of the cuboid at term. Diagnosis of full maturity is made on the basis of ossification of the distal epiphysis of the femur (95 per cent of all cases); ossification of the proximal epiphysis of the tibia (60 per cent), and ossification of the cuboid (60 per cent). From this it is noted that, although individual variations are often present, in general by the radiologic determination of the position of the child, the mensuration of the head and spine, and the presence or absence of ossification centers, the intrauterine age of the child can be quite accurately determined. However, the procedure is a laboratory one, and, as with all laboratory procedures, must be integrated with other physiological factors for accurate diagnosis.

L. B. WINKELSTEIN

Toxemia

Mukherjee, C. L., and Govan, A. D. T.: Nitrogen Metabolism in Hypertensive Toxaemia of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **58:** 701, 1951.

Nitrogen balance studies were made in one normal pregnant woman and 3 patients with hypertensive toxemia. In the normal pregnant woman there was a marked storage of nitrogen and positive nitrogen balance. In the patients with hypertensive toxemia, there was very little nitrogen storage and, because of loss of protein in the urine, the nitrogen balance was negative. It is suggested that the reduction in nitrogen storage in hypertensive toxemia may be due either to increased protein catabolism or to a reduction of the patient's capacity to utilize the assimilated nitrogen. In the toxemia of pregnancy, the protein intake must be increased to compensate for the loss due to the albuminuria and the probable increase in protein catabolism. Adequate carbohydrate, because it is protein sparing, must also be included in the diet to establish a positive nitrogen balance.

HARVEY B. MATTHEWS

Item

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and pathological, for all candidates will be held at the Edgewater Beach Hotel, Chicago, Ill., by the entire Board from May 17, 1953, through May 24, 1953. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Requests for re-examination in Part II must be made prior to Feb. 1, 1953, submitting data regarding additional training or experience and medical school or hospital staff appointments acquired in the interim.

Candidates currently applying for admission to the examinations for certification are required to submit a list of all patients for whom they have been solely responsible admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application, with the diagnosis, pathological diagnosis, nature of treatment, and end result.

Dr. Lawrence M. Randall, who is Assistant Secretary of the American Board of Obstetrics and Gynecology, is in charge of all matters pertaining to Residency Training. All requests for information to be supplied by the American Board of Obstetrics and Gynecology relative to residency training should be addressed to:

LAWRENCE M. RANDALL, M.D.
ASSISTANT SECRETARY, AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
MAYO CLINIC
ROCHESTER, MINN.

Application forms for Appraisal of Incomplete Training, for Certification, and requests for current Bulletins should be made to:

ROBERT L. FAULKNER, M.D.
SECRETARY, AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO